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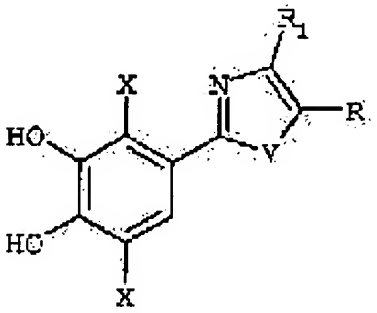
(54) 2-(2,5-DIHALOGEN-3,4-DIHYROXYPHENYL)AZOLE AND MEDICINAL COMPOSITION CONTAINING THE SAME

(57)Abstract:

PROBLEM TO BE SOLVED: To provide a prophylactic and therapeutic medicine for diabetes of a new type that has excellent protein tyrosine phosphatase 1B(PTP1B) inhibitory action and can directly improve the action of insulin.

SOLUTION: The objective prophylactic and therapeutic agent is 2-(2,5- dihalogen-3,4-dihydroxyphenyl)azole represented by general formula [I] (wherein one of R or R1 is H, the other is an aryl group which may substituted or a 5- or 6-membered heteroaryl group which may be substituted; X is a halogen atom; Y is a sulfur or oxygen atom or the like) or pharmaceutically acceptable salt thereof.



[I]

LEGAL STATUS

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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] This invention relates to the remedy constituent which comes to contain the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound which has protein thyrosin phosphatase 1B (PTP1B;Protein Tyrosine Phosphatase 1B) inhibition activity in more detail, or its remedy about new 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound.
[0002]
[Description of the Prior Art] Diabetes mellitus is a disease which causes various metabolic errors which made the chronic hyperglycemia condition the cardinal symptom, and shows various symptoms based on hyperglycemia, such as thirst, polyposia, polyuria, and a loss weight. Moreover, if such a hyperglycemia condition continues for a long time, starting various complication, such as myocardial infarction based on a retinopathy, a nephropathy, neuropathy, and arteriosclerosis and cerebral infarction, is also known.
[0003] The I-beam diabetes mellitus which will cause absolute insulin lack by breakage and destruction of beta cells of pancreas if diabetes mellitus divides roughly (IDDM; insulin-dependent diabetes mellitus), The special diabetes mellitus whose symptoms are secondarily shown in connection with II type <2> diabetes mellitus (NIDDM; non-insulin dependent diabetes mellitus) which causes relative insulin lack, abnormalities, other diseases of a gene, etc. by insulin resistance and insulin secretion lowering, the inside of those who were divided into four molds of pregnancy diabetes, and were diagnosed as II type <2> diabetes mellitus at the beginning of the onset -- progress -- gradually -- insulin secretion ability -- falling -- just -- being alike -- it may result in I-beam diabetes mellitus
[0004] By the way, if a living body's saccharometabolism is seen, as opposed to the ingredient used as a living body's energy source or a constituent being incorporated inside of the body intermittently, the brain will consume the glucose without an intermission. In such a situation, the blood sugar level is kept almost constant and the interaction of exchanges, such as a metabolic turnover in the hormone and the organ concerning blood sugar regulation and sugar between organs, makes such blood sugar regulation possible. It is thought that the operation of the insulin which is hormone especially concerning blood sugar regulation is important also in it, and the failure, i.e., insulin resistance, and insulin secretion lowering are participating in diabetes mellitus deeply.
[0005] An insulin is secreted from beta cells of pancreas, and after combining with the insulin receptor in the film front face of a skeletal muscle cell or a fat cell which is the target cell, self-phosphorylation of the thyrosin residue of an intracellular domain is carried out. Then, phosphorylation of the thyrosin residue which is the substrates of an insulin receptor, such as IRS (insulin receptor substrate) and APS (adapter protein containing PH and SH2 domain), is carried out, when an PI3 kinase-Akt path is activated, a glucose transporter is made to shift to up to a cell membrane, incorporation of a glucose takes place, and the sugar concentration in blood falls. On the other hand, the thyrosin phosphatase which performs thyrosin dephosphorization which adjusts the intracellular signaling by this insulin to

negative also existed, and that activation is controlled. Thus, although thyrosin phosphorylation is bearing the central role in an insulin operation, if thyrosin phosphorylation considers being decided by balance of the activity of the thyrosin phosphatase which is the tyrosine kinase and phosphatase which are phosphorylated enzyme, it will be thought that thyrosin phosphatase has played the important modulatory role which participates in insulin signal transfer directly with tyrosine kinase.
[0006] Although current and thyrosin phosphatase form a big gene family and about seventy or more kinds of isozymes are reported, it is thought also in it that protein thyrosin phosphatase 1B (PTP1B;Protein Tyrosine Phosphatase 1B) is phosphatase specific to insulin signal transfer. It is admitted that the gene expression of PTP1B increases by high grape-sugar culture especially. The intracellular localization changes and an insulin receptor and the thyrosin phosphorylation of IRS-1 decrease. guiding insulin resistance (J.Biol.Chem, 270:7724-7730, and 1995;J.Biochem. (Tokyo) --) 123 : The failure of the translocation of the sugar transporter GLUT4 was carried out by installation of the wild type of 813-820, 1998, and PTP1B, and the effectiveness was not accepted in a phosphatase activity deficit mutant, Furthermore, insulin susceptibility reinforces by the knockout mouse of PTP1B recently. Moreover, since it was reported that it became obesity resistance to a high fat food (Science, 283:1544-1548, 1999), it is suggested that this enzyme can become one target of an insulin resistance improvement. It is admitted that the vanadium acid known shows an insulin resistance improvement effect in an animal experiment etc. actually from before as thyrosin phosphatase inhibitor.
[0007] Therefore, such thyrosin phosphatase, especially the drug which controls and/or checks abnormality activation of PTP1B improve insulin susceptibility, insulin resistance, and/or glucose tolerance, and can serve as diabetic medicine new type which returns the intracellular signaling of an insulin to normal. Moreover, the application to various disease remedies, such as obesity and a neurodegenerative disease, is also expectable.
[0008] It continues till recently and various reports are made about the compound aiming at treating diseases, such as diabetes mellitus, by checking protein thyrosin phosphatase in this way. For example, WO The phosphonic acid derivative which has PTP-1B inhibitory action is indicated by the No. 00/17211 official report. However, in this official report, the publication of the purport which suggests it is not found as well as disclosure of the compound which has the structure like this invention compound, either.
[0009] The aryl acrylic-acid derivative useful as a protein thyrosin phosphatase inhibitor is indicated by the Patent Publication Heisei No. 508919 [11 to] official report (US No. 5,770,620 official report). However, in this official report, the publication of the purport which suggests it is not found as well as disclosure of the compound which has the structure like this invention compound, either.
[0010] WO The thiazole compound which has protein thyrosin phosphatase inhibitory action is indicated by the No. 98/27092 official report (US No. 6,080,772 official report). However, in this official report, the publication of the purport which suggests it is not found as well as disclosure of the compound which has the structure like this invention compound, either.
[0011] WO In a No. 99/58522 official report, a [2 and 3-naphth B] HETEROARU-4-IRU derivative WO In a No. 99/58511 official report, OKISA / thiazole-aryl-carboxylic acid WO A No. 99/58521 official report and US In a No. 6,110,962 official report, the 11-aryl-[benzoB] [2 and 3-naphth D] furan and 11-aryl-[benzoB] [2 and 3-naphth D] thiophene WO In a No. 99/58518 official report, a biphenyl-oxo--acetic acid WO In a No. 99/61419 official report, 2, 3, and 5-permutation biphenyl WO In a No. 99/58520 official report, a biphenyl-sulfonyl-aryl-carboxylic acid WO In a No. 99/61435 official report, benzothiophene, benzofuran, and Indore US In a No. 6,103,708 official report, a furan, benzofuran, and a thiophene US In a No. 6,110,963 official report, an aryl-oxo--acetic acid US In a No. 6,001,867 official report, a 1-aryl-dibenzo thiophene US 4-PENTA [aryl-1-OKISA-9-thia-cyclo] [B] fluorene is indicated by it at the No. 6,057,316 official report noting that a benzophenone has protein thyrosin phosphatase inhibitory action in US No. 6,063,815 official report, respectively. However, in these official reports, the publication of the purport which suggests it is not found as well as disclosure of the compound which has the structure like this invention compound, either.
[0012] Moreover, many things are reported also about the azole compound like this invention. For

example, JP,5-51318,A, JP,10-101562,A, WO No. 92/09586 official report and EP 0 934 A thiazole and oxazole compounds, such as a 2-(3, 4-dimethoxy phenyl)-4-phenyl thiazole, are useful in a No. 937 official report as an active oxygen inhibitor, and a diabetes-mellitus therapy agent etc. is indicated as the application. However, this official report compound is useful as an active oxygen inhibitor, and the publication of the purport which suggests it is not found as well as the disclosure about the usefulness as a PTP1B inhibitor with which action mechanisms differ, either. Or it differs. moreover, the same [as R1 and R3] to the claim of this official report -- The phenyl group which it can choose out of the group which consists of an alkoxy group, a hydroxyl group, a halogen atom, etc., and has had five **** machines from 1; although the hydrogen atom; phenyl group etc. is defined as R2, respectively, the heterocycle radical which may be permuted by the alkyl group etc. In this official report description, the publication of the example which supports the manufacture and the activity of a compound which have the structure like this invention compound, i.e., 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole structure, is not found.

[0013] An oxazole derivative and thiazole derivatives, such as 2-(3, 5-G tert-butyl-4-hydroxyphenyl)-4-(4-dimethylamino phenyl)-1 and 3-oxazole, are indicated by JP,61-40276,A. However, this official report compound is useful as a detection reagent of a hydrogen peroxide and a peroxidase active substance, and the publication of the purport which suggests it is not found as well as the disclosure about the usefulness as a PTP1B inhibitor, either. Moreover, in this official report, neither disclosure of the compound which has the structure like this invention compound, nor the publication of the purport which suggests it is found.

[0014] WO Thiazole derivatives, such as a 2-(3-cyclopenthyloxy-4-methoxypheny)-4-phenyl thiazole, are indicated by the No. 98/08830 official report. However, in this reference, the publication of the purport which suggests it is not found as well as disclosure of the compound which has the structure like this invention compound, either. Moreover, this official report compound is useful as an alternative inhibitor of Phosphodiesterase IV, and neither disclosure nor the publication of the purport which suggests it is found about the usefulness as a PTP1B inhibitor like this invention.

[0015]

[Problem(s) to be Solved by the Invention] this invention person etc. came to complete a header and this invention for the compound useful as diabetic medicine new type which can show the PTP1B inhibition activity excellent in the compound which has 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole structure, namely, can improve an insulin operation directly, as a result of inquiring wholeheartedly that the compound which checks PTP1B specifically like the above should be offered.

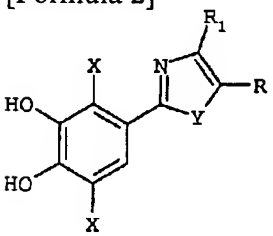
[0016]

[Means for Solving the Problem] That is, this invention relates to the remedy constituent which comes to contain the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound shown in following (1) thru/or (38), or its remedy, and these 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound.

[0017] (1) General formula [I]

[0018]

[Formula 2]



[I]

[0019] R or one side of R1 is a hydrogen atom among [type. Another side It is the hetero aryl group of 1 5 which it has three pieces and which may be permuted thru/or 6 members about the heteroatom chosen from the aryl group which may be permuted or a nitrogen atom, an oxygen atom, and a sulfur atom. It is

the salt which X is a halogen atom and can permit Y on a sulfur atom, an oxygen atom, 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound expressed with] which is -NR2- (it is here and R2 is a hydrogen atom or C1-4 alkyl group), or its remedy.
[0020] (2) R or one side of R1 is a hydrogen atom, and another side is chosen from the following -- you may permute by the same or 1 which may differ thru/or three substituents -- An aryl group or a nitrogen atom, The heteroatom chosen from an oxygen atom and a sulfur atom 1 -- or Even if the hetero aryl group permutation of 5 which it has three pieces thru/or the 6 members is carried out Good C1-4 alkyl group; even if it permutes good C1-4 alkoxy-group; -- C1-4 alkylthio-group; -- C1-4 alkyl sulfinyl group; -- C1-4 alkyl sulfonyl group; -- amino sulfonyl group; -- halogen atom; -- nitro group; -- cyano group; -- carboxyl group; -- C2-5 alkoxy carbonyl group; -NR3R4;-N (R5) CONR3R4;-N(R5) COR6;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, It is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members. R5 is a hydrogen atom or C1-4 alkyl group, and R6 is C1-4 alkyl group or C1-4 alkoxy group -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (1) publication, or its remedy.
[0021] (3) R or one side of R1 is a hydrogen atom. The aryl group C1-4 alkoxy-group; halogen atom; nitro group; cyano group as which another side is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (2) publication, or its remedy.
[0022] The aryl group methoxy group as which R or one side of R1 is a hydrogen atom, and another side is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; (4) A fluorine atom, bromine atom; -- nitro group; -- cyano group; -- carboxyl group; -- a methoxycarbonyl group -- Ethoxycarbonyl radical; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (3) publication which are a methyl carbamoyl group, a dimethyl carbamoyl group, a pyrrolidinyl carbonyl group, and a morpholino carbonyl radical, or its remedy.
[0023] (5) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above (1) whose R1 is a hydrogen atom thru/or the above-mentioned (4) publication, or its remedy.
[0024] (6) The phenyl group C1-4 alkoxy-group; halogen atom; nitro group; cyano group as which R is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (3) publication, or its remedy.
[0025] (7) R -- the following -- from -- choosing -- having -- the same -- or -- differing -- **** -- one -- or -- three -- a piece -- a substituent -- permuting -- having -- **** -- a phenyl group -- C -- one - four -- an alkoxy group --; -- a halogen -- an atom --; -- a nitro group --; -- a cyano group --; -- a carboxyl group --; -- C -- two - five -- alkoxy one -- a carbonyl group -- it is -- the above -- (-- six --) -- a publication -- two - 2, 5-dihalogen -3, 4-dihydroxy phenyl) -- azole -- a compound -- or -- the -- a remedy -- a top -- approving -- obtaining -- a salt .
[0026] (8) R -- the following -- from -- choosing -- having -- the same -- or -- differing -- **** -- one -- or -- three -- a piece -- a substituent -- permuting -- having -- **** -- a phenyl group -- a methoxy group

--; -- a bromine -- an atom --; -- a nitro group --; -- a cyano group --; -- a carboxyl group --; -- a methoxycarbonyl group -- ethoxycarbonyl -- a radical -- it is -- the above -- (-- seven --) -- a publication -- two - (2, 5-dihalogen -3, 4-dihydroxy phenyl) -- azole -- a compound -- or -- the -- a remedy -- a top -- approving -- obtaining a salt -- .

[0027] R (9) A phenyl group, 2-methoxypheny radical, 3-methoxypheny radical, 4-methoxypheny radical, 4-BUROMO phenyl group, 4-nitrophenyl group, 4-cyanophenyl radical, 3-carboxyphenyl radical, 4-carboxyphenyl radical, 4-ethoxycarbonyl phenyl group, a 3-carboxy-4-methoxycarbonyl phenyl group, The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (8) publication which is a 4-methoxy-3-methoxycarbonyl phenyl group, or its remedy.

[0028] (10) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (9) publication whose R is a phenyl group and 4-carboxyphenyl radical, or its remedy.

[0029] (11) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above (1) whose R is a hydrogen atom thru/or the above-mentioned (4) publication, or its remedy.

[0030] (12) The phenyl group C1-4 alkoxy-group; halogen atom; nitro group; cyano group as which R1 is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (3) publication, or its remedy.

[0031] (13) The phenyl group C1-4 alkoxy-group; halogen atom with which R1 is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (12) publication, or its remedy.

[0032] (14) R -- one -- the following -- from -- choosing -- having -- the same -- or -- differing -- **** -- one -- or -- three -- a piece -- a substituent -- permuting -- having -- **** -- a phenyl group -- a methoxy group --; -- a fluorine -- an atom --; -- a carboxyl group --; -- a methoxycarbonyl group -- ethoxycarbonyl -- a radical --; -- methyl -- a carbamoyl group -- dimethyl -- a carbamoyl group -- pyrrolidinyl -- a carbamoyl group -- morpholino -- a carbamoyl group -- it is -- the above -- (-- 13 --) -- a publication -- two - 2, 5-dihalogen -3, 4-dihydroxy phenyl) -- azole -- a compound -- or -- the -- a remedy -- a top -- approving -- obtaining -- a salt -- .

[0033] R1 (15) A phenyl group, 4-methoxypheny radical, 4-fluoro phenyl group, 4-carboxyphenyl radical, 4-ethoxycarbonyl phenyl group, 2, 4-dimethoxy phenyl group, 2, 5-dimethoxy phenyl group, a 3-carboxy-4-methoxypheny radical, A 4-methoxy-3-methoxycarbonyl phenyl group, a 4-methoxy-3-(methyl carbamoyl) phenyl group, A 3-(dimethyl carbamoyl)-4-methoxypheny radical, a 4-methoxy-3-(1-pyrrolidinyl carbonyl) phenyl group, The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (14) publication which is a 4-methoxy-3-(morpholino carbonyl) phenyl group, or its remedy.

[0034] (16) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (15) publication whose R1 is a 4-methoxy-3-methoxycarbonyl phenyl group, or its remedy.

[0035] (17) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above (1) whose Y is a sulfur atom thru/or the above-mentioned (16) publication, or its

remedy.
[0036] (18) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above (1) whose Y is an oxygen atom thru/or the above-mentioned (16) publication, or its remedy.
[0037] (19) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above (1) whose Y is -NR2- (here, R2 is a hydrogen atom or C1-4 alkyl group) thru/or the above-mentioned (16) publication, or its remedy.
[0038] (20) R -- the following -- from -- choosing -- having -- the same -- or -- differing -- **** -- one -- or -- three -- a piece -- a substituent -- permuting -- having -- **** -- a phenyl group -- C -- one - four -- an alkoxy group --; -- a halogen -- an atom --; -- a nitro group --; -- a cyano group --; -- a carboxyl group --; -- C -- two - five -- alkoxy one -- a carbonyl group -- it is -- R -- one -- a hydrogen atom -- it is -- Y -- sulfur -- an atom -- it is -- the above -- (-- three --) -- a publication -- two - (2, 5-dihalogen -3, 4-dihydroxy phenyl) -- azole -- a compound -- or -- the -- a remedy -- a top -- approving -- obtaining -- a salt .
[0039] (21) R -- the following -- from -- choosing -- having -- the same -- or -- differing -- **** -- one -- or -- three -- a piece -- a substituent -- permuting -- having -- **** -- a phenyl group -- a methoxy group --; -- a bromine -- an atom --; -- a nitro group --; -- a cyano group --; -- a carboxyl group --; -- a methoxycarbonyl group -- ethoxycarbonyl -- a radical -- it is -- R -- one -- a hydrogen atom -- it is -- Y -- sulfur -- an atom -- it is -- the above -- (-- 20 --) -- a publication -- two -- - 2, 5-dihalogen -3, 4-dihydroxy phenyl) -- azole -- a compound -- or the -- a remedy -- a top -- approving -- obtaining -- a salt .
[0040] (22) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (21) publication whose R is a phenyl group or 4-carboxyphenyl radical, whose R1 is a hydrogen atom, and whose Y is a sulfur atom, or its remedy.
[0041] (23) The phenyl group C1-4 alkoxy-group; halogen atom with which R is a hydrogen atom and R1 is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (3) publication whose Y is a sulfur atom, or its remedy.
[0042] (24) R -- a hydrogen atom -- it is -- R -- one -- the following -- from -- choosing -- having -- the same -- or -- differing -- **** -- one -- or -- three -- a piece -- a substituent -- permuting -- having -- **** -- a phenyl group -- a methoxy group --; -- a fluorine -- an atom --; -- a carboxyl group --; -- a methoxycarbonyl group -- ethoxycarbonyl -- a radical --; -- methyl -- a carbamoyl group -- dimethyl -- a carbamoyl group -- pyrrolidinyl -- a carbonyl group -- morpholino carbonyl -- a radical -- it is -- Y -- sulfur -- an atom -- it is -- the above -- (-- 23 --) -- a publication -- two -- - 2, 5-dihalogen -3, 4-dihydroxy phenyl) -- azole -- a compound -- or -- the -- a remedy -- a top -- approving -- obtaining -- a salt .
[0043] (25) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (24) publication whose R is a hydrogen atom, whose R1 is a 4-methoxy-3-methoxycarbonyl phenyl group, and whose Y is a sulfur atom, or its remedy.
[0044] (26) R -- the following -- from -- choosing -- having -- the same -- or -- differing -- **** -- one -- or -- three -- a piece -- a substituent -- permuting -- having -- **** -- a phenyl group -- C -- one - four -- an alkoxy group --; -- a halogen -- an atom --; -- a nitro group --; -- a cyano group --; -- a carboxyl group --; -- C -- two - five -- alkoxy one -- a carbonyl group -- it is -- R -- one -- a hydrogen atom -- it is -- Y -- oxygen -- an atom -- it is -- the above -- (-- three --) -- a publication -- two - (2, 5-dihalogen -3, 4-dihydroxy phenyl) -- azole -- a compound -- or -- the -- a remedy -- a top -- approving -- obtaining -- a salt .
[0045] (27) R -- the following -- from -- choosing -- having -- the same -- or -- differing -- **** -- one --

or -- three -- a piece -- a substituent -- permuting -- having -- **** -- a phenyl group -- a methoxy group --; -- a bromine -- an atom --; -- a nitro group --; -- a cyano group --; -- a carboxyl group --; -- ethoxycarbonyl -- a radical -- it is -- R -- one -- a hydrogen atom -- it is -- Y -- oxygen -- an atom -- it is -- the above -- (-- 26 --) -- a publication -- two - (2, 5-dihalogen -3, 4-dihydroxy phenyl) -- azole -- a compound -- or -- the a remedy -- a top -- approving -- obtaining -- a salt .

[0046] (28) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above (1) whose X is a chlorine atom or a bromine atom thru/or the above-mentioned (27) publication, or its remedy.

[0047] (29) A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl thiazole, A 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-naphthyl) thiazole, A 5-(4-biphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-nitrophenyl) thiazole, A 5-(4-BUROMO phenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 5-(4-cyanophenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(3-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-methoxypheny) thiazole, A 5-(3-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo 3, 4-dihydroxy phenyl)-5-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 5-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-phenyl thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) thiazole, A 5-(4-carboxyphenyl)-2-(2, 5-dichloro -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-phenyl thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-ethoxycarbonyl phenyl) thiazole, A 4-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(2, 4-dimethoxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(2, 5-dimethoxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-fluoro phenyl) thiazole, A 4-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo 3, 4-dihydroxy phenyl)-4-[3-(dimethyl carbamoyl)-4-methoxypheny] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(1-pyrrolidinyl carbonyl) phenyl] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(methyl carbamoyl) phenyl] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(morpholino carbonyl) phenyl] thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 4-(3-carboxy-4-methoxypheny)-2-(2, 5-dichloro -3, 4-dihydroxy phenyl) thiazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) oxazole, 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-naphthyl) oxazole, 5-(4-biphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-nitrophenyl) oxazole, 5-(4-BUROMO phenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, And the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (1) publication chosen from the group which consists of 5-(4-cyanophenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, or its remedy.

[0048] (30) A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl thiazole, A 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-naphthyl) thiazole, A 5-(4-biphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-nitrophenyl) thiazole, A 5-(4-BUROMO phenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 5-(4-cyanophenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(3-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-methoxypheny)

thiazole, A 5-(3-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo 3, 4-dihydroxy phenyl)-5-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 5-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-phenyl thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) thiazole, A 5-(4-carboxyphenyl)-2-(2, 5-dichloro -3, 4-dihydroxy phenyl) thiazole, And 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (29) publication chosen from the group which consists of a 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) thiazole Or the salt which can be permitted on the remedy.

[0049] (31) A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-phenyl thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-ethoxycarbonyl phenyl) thiazole, A 4-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(2, 4-dimethoxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(2, 5-dimethoxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-fluoro phenyl) thiazole, A 4-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo 3, 4-dihydroxy phenyl)-4-[3-(dimethyl carbamoyl)-4-methoxypheny] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(1-pyrrolidinyl carbonyl) phenyl] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(methyl carbamoyl) phenyl] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(morpholino carbonyl) phenyl] thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, And 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (29) publication chosen from the group which consists of a 4-(3-carboxy-4-methoxypheny)-2-(2, 5-dichloro -3, 4-dihydroxy phenyl) thiazole Or the salt which can be permitted on the remedy.

[0050] (32) 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) oxazole, 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-naphthyl) oxazole, 5-(4-biphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-nitrophenyl) oxazole, 5-(4-BUROMO phenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, And the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (29) publication chosen from the group which consists of 5-(4-cyanophenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, or its remedy.

[0051] (33) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (30) publication which is a 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl thiazole, or its remedy.

[0052] (34) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (30) publication which is a 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, or its remedy.

[0053] (35) The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above-mentioned (31) publication which is a 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, or its remedy.

[0054] (36) The remedy constituent which becomes considering the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above (1) thru/or the above-mentioned (35) publication, or its remedy as an active principle.

[0055] (37) The protein thyrosin phosphatase 1B inhibitor which becomes considering the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above (1) thru/or the above-mentioned (35) publication, or its remedy as an active principle.

[0056] (38) Diabetic medicine which becomes considering the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound of the above (1) thru/or the above-mentioned (35) publication, or its remedy as an active principle. Here, the definition of each substituent used in this description is as follows.

[0057] "C1-4 alkyl group" means the carbon atomic number 1 thru/or four alkyl groups which may be straight chains or may be branching-like, and is specifically a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, etc. Preferably, they are a methyl group and an ethyl group.
[0058] The same or the above-mentioned C1-4 alkyl group which may be permuted by 1 which may differ thru/or three substituents, for example, halogen atom; hydroxyl-group; amino-group;C1-4 alkylamino radical; G C1-4 alkylamino radical;C1-4 alkoxy group etc., is meant as "the C1-4 alkyl group which may be permuted." Specifically, they are a trifluoromethyl radical, a hydroxymethyl group, an aminomethyl radical, 2-aminoethyl radical, a methylamino methyl group, an ethylamino methyl group, 2-(methylamino) ethyl group, 2-(ethylamino) ethyl group, a dimethyl aminomethyl radical, a diethyl aminomethyl radical, 3-(dimethylamino) propyl group, a methoxymethyl radical, an ethoxy methyl group, 2-methoxy ethyl group, 2-ethoxyethyl radical, etc.
[0059] "C1-4 alkoxy group" means the alkoxy group which has the above-mentioned C1-4 alkyl group, and is specifically a methoxy group, an ethoxy radical, a propoxy group, an isopropoxy group, a butoxy radical, an iso butoxy radical, a sec-butoxy radical, a tert-butoxy radical, etc. Preferably, they are a methoxy group and an ethoxy radical.
[0060] The same or the above-mentioned C1-4 alkyl group which may be permuted by 1 which may differ thru/or three substituents, for example, halogen atom; hydroxyl-group; amino-group;C1-4 alkylamino radical; G C1-4 alkylamino radical;C1-4 alkoxy group etc., is meant as "the C1-4 alkoxy group which may be permuted." Specifically, they are a trifluoro methoxy group, 2-aminoethoxy radical, a methylamino methoxy group, an ethylamino methoxy group, a 2-(methylamino) ethoxy radical, a 2-(ethylamino) ethoxy radical, a dimethylamino methoxy group, a diethylamino methoxy group, 3-(dimethylamino) propoxy group, a methoxy methoxy group, an ethoxy methoxy group, a 2-methoxyethoxy radical, a 2-ethoxy ethoxy radical, etc.
[0061] "C1-4 alkylthio group" means the alkylthio group which has the above-mentioned C1-4 alkyl group, and is specifically a methylthio radical, an ethyl thio radical, a propyl thio radical, an isopropyl thio radical, a butyl thio radical, an isobutyl thio radical, a sec-butyl thio radical, a tert-butyl thio radical, etc. Preferably, they are a methylthio radical and an ethyl thio radical.
[0062] A "C1-4 alkyl sulfinyl group" means the alkyl sulfinyl group which has the above-mentioned C1-4 alkyl group, and is specifically a methyl sulfinyl group, an ethyl sulfinyl group, a propyl sulfinyl group, an isopropyl sulfinyl group, a butyl sulfinyl group, an isobutyl sulfinyl group, a sec-butyl sulfinyl group, a tert-butyl sulfinyl group, etc. Preferably, they are a methyl sulfinyl group and an ethyl sulfinyl group.
[0063] A "C1-4 alkyl sulfonyl group" means the alkyl sulfonyl group which has the above-mentioned C1-4 alkyl group, and is specifically a methyl sulfonyl group, an ethyl sulfonyl group, a propyl sulfonyl group, an isopropyl sulfonyl group, a butyl sulfonyl group, an isobutyl sulfonyl group, a sec-butyl sulfonyl group, a tert-butyl sulfonyl group, etc. Preferably, they are a methyl sulfonyl group and an ethyl sulfonyl group.
[0064] A "C2-5 alkoxy carbonyl group" means the alkoxy carbonyl group which has the above-mentioned C1-4 alkoxy group, and is specifically a methoxycarbonyl group, an ethoxycarbonyl radical, a propoxy carbonyl group, an isopropoxycarbonyl radical, a butoxycarbonyl radical, an iso butoxycarbonyl radical, a sec-butoxycarbonyl radical, a tert-butoxycarbonyl radical, etc. Preferably, they are a methoxycarbonyl group and an ethoxycarbonyl radical.
[0065] "Halogen atoms" is specifically a fluorine atom, a chlorine atom, a bromine atom, etc.
[0066] The "aryl groups" in the aryl group which may be permuted is specifically phenyl, a naphthyl group, a biphenyl radical, etc., and is phenyl groups preferably.
[0067] ["you permuting" in the aryl group which may be permuted, and] The same or 1 which may differ thru/or three substituents, For example, even if the above-mentioned is permuted Good C1-4 alkyl group; even if the above-mentioned is permuted Good C1-4 alkoxy-group; above-mentioned C1-4 alkylthio-group; -- above-mentioned C1-4 alkyl sulfinyl group; -- above-mentioned C1-4 alkyl sulfonyl group; -- amino sulfonyl group; -- above-mentioned halogen atom; -- nitro group; -- cyano group; --

carboxyl group; -- above-mentioned C2-5 alkoxy carbonyl group; -NR three R4 (here) as R3 and R4 being defined by above-mentioned claim 2 -- it is -- amino-group;-N(R5) CONR three R4 (it is here) shown as R3, R4, and R5 being defined by above-mentioned claim 2 -- it is -- ureido radical;-N(R5) COR6 (it is here) shown as R5 and R6 being defined by above-mentioned claim 2 -- it is -- acylamino radical;-CONR three R4 (it is here) shown as R3 and R4 being defined by above-mentioned claim 2 -- it is -- it means that you may permute by the carbamoyl group shown, and means that you may permute by 1 thru/or two substituents preferably.

[0068] The heteroatom chosen from a nitrogen atom, an oxygen atom, and a sulfur atom with "the hetero aryl group of 5 thru/or 6 members" in the hetero aryl group of 1 5 which it has three pieces and which may be permuted thru/or 6 members The aromatic series heterocycle radical of 5 which has 1 thru/or three heteroatoms chosen from the group which consists of a nitrogen atom, an oxygen atom, and a sulfur atom thru/or 6 members is meant. Specifically, they are an oxadiazolyl radical, a thiadiazolyl radical, a thoria ZORIRU radical, an oxazolyl radical, a thiazolyl radical, an imidazolyl radical, a pyrazolyl radical, a pyrrolyl radical, a furil radical, a thienyl group, a thoriadinyl group, a pyrazinyl radical, a pilus DAJINIRU radical, a pyrimidinyl group, a pyridyl radical, etc.

[0069] The heteroatom chosen from a nitrogen atom, an oxygen atom, and a sulfur atom ["you permuting" in the hetero aryl group of 1 5 which it has three pieces and which may be permuted thru/or 6 members, and] The same or 1 which may differ thru/or three substituents, For example, even if the above-mentioned is permuted Good C1-4 alkyl group; even if the above-mentioned is permuted Good C1-4 alkoxy-group; above-mentioned C1-4 alkylthio-group; -- above-mentioned C1-4 alkyl sulfinyl group; -- above-mentioned C1-4 alkyl sulfonyl group; -- amino sulfonyl group; -- above-mentioned halogen atom; -- nitro group; -- cyano group; -- carboxyl group; -- above-mentioned C2-5 alkoxy carbonyl group; -NR three R4 (here) as R3 and R4 being defined by above-mentioned claim 2 -- it is -- amino-group;-N(R5) CONR three R4 (it is here) shown as R3, R4, and R5 being defined by above-mentioned claim 2 -- it is -- ureido radical;-N(R5) COR6 (it is here) shown as R5 and R6 being defined by above-mentioned claim 2 -- it is -- acylamino radical;-CONR three R4 (it is here) shown as R3 and R4 being defined by above-mentioned claim 2 -- it is -- it means that you may permute by the carbamoyl group shown, and means that you may permute by 1 thru/or two substituents preferably.

[0070] "The heterocycle radical of 5 which may contain the heteroatom which becomes together with the nitrogen atom which R3 and R4 combine, and is further chosen from a nitrogen atom, an oxygen atom, and a sulfur atom thru/or 6 members" The nitrogen atom which R3 and R4, and they combine becomes together. Further A nitrogen atom, The heterocycle radical of the aromatic series of 1 5 which you may have three pieces thru/or 6 members, or non-aromatic series is meant for the heteroatom chosen from an oxygen atom and a sulfur atom. Specifically Aromatic series heterocycle radicals, such as a thoria ZORIRU radical, an imidazolyl radical, a pyrazolyl radical, and a pyrrolyl radical, Or they are non-aromatic series heterocycle radicals, such as a pyrrolidinyl radical, a morpholino radical, a piperazinyl radical, a piperidyl radical, a pylori nil radical, an imidazolidinyl radical, an imidazo RINIRU radical, a PIRAZORIJINIRU radical, and a PIRAZORINIRU radical, etc. Preferably, they are a pyrrolidinyl radical and a morpholino radical. Hereafter, although stated more concretely, it is not necessarily limited below.

[0071] As an "aryl group" of the aryl group in R or R1 which may be permuted, it is a phenyl group preferably.

[0072] It means that you may permute by 1 thru/or three substituents preferably as the aryl group in R or R1 which may be permuted "being permuted", and means that you may permute by 1 thru/or two substituents preferably especially.

[0073] As a "substituent" of the aryl group in R or R1 which may be permuted Even if the above-mentioned is permuted preferably Good C1-4 alkyl group; even if the above-mentioned is permuted Good C1-4 alkoxy-group; above-mentioned C1-4 alkylthio-group; -- above-mentioned C1-4 alkyl sulfinyl group; -- above-mentioned C1-4 alkyl sulfonyl group; -- alkyl sulfonyl group; -- above-mentioned halogen atom; -- nitro group; -- cyano group; -- carboxyl group; -- above-mentioned C2-5 alkoxy carbonyl group; -NR three R4 (here) as R3 and R4 being defined by above-mentioned claim 2 --

it is -- amino-group;-N(R5) CONR three R4 (it is here) shown as R3, R4, and R5 being defined by above-mentioned claim 2 -- it is -- ureido radical;-N(R5) COR6 (it is here) shown as R5 and R6 being defined by above-mentioned claim 2 -- it is -- acylamino radical;-CONR three R4 (it is here) shown as R3 and R4 being defined by above-mentioned claim 2 -- it is -- it is the carbamoyl group shown and is C1-4 alkoxy-group; halogen atom; nitro group; cyano group; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 especially preferably. More specifically, they are a methoxy group, a fluorine atom, a bromine atom, a nitro group, a cyano group, a carboxyl group, a methoxycarbonyl group, an ethoxycarbonyl radical, a methyl carbamoyl group, a dimethyl carbamoyl group, a pyrrolidinyl carbonyl group, and a morpholino carbonyl radical.

[0074] As "an aryl group which may be permuted" in R or R1 Preferably A phenyl group, 2-naphthyl group, 4-biphenyl radical, 2-methoxypheny radical, 3-methoxypheny radical, 4-methoxypheny radical, 4-fluoro phenyl group, 4-BUROMO phenyl group, 4-nitrophenyl group, 4-cyanophenyl radical, 3-carboxyphenyl radical, 4-carboxyphenyl radical, 4-ethoxycarbonyl phenyl group, 2, 4-dimethoxy phenyl group, 2, 5-dimethoxy phenyl group, a 3-carboxy-4-methoxycarbonyl phenyl group, A 4-methoxy-3-methoxycarbonyl phenyl group, a 4-methoxy-3-(methyl carbamoyl) phenyl group, A 3-(dimethyl carbamoyl)-4-methoxypheny radical, a 4-methoxy-3-(1-pyrrolidinyl carbonyl) phenyl group, It is a 4-methoxy-3-(morpholino carbonyl) phenyl group, and they are a phenyl group, 4-carboxyphenyl radical, and a 4-methoxy-3-methoxycarbonyl phenyl group especially preferably.

[0075] As "an aryl group which may be permuted" in the case of being the aryl group by which R may be permuted Preferably A phenyl group, 2-naphthyl group, 4-biphenyl radical, 2-methoxypheny radical, 3-methoxypheny radical, 4-methoxypheny radical, 4-BUROMO phenyl group, 4-nitrophenyl group, 4-cyanophenyl radical, 3-carboxyphenyl radical, It is 4-carboxyphenyl radical, 4-ethoxycarbonyl phenyl group, a 3-carboxy-4-methoxypheny radical, and a 4-methoxy-3-methoxycarbonyl group, and they are a phenyl group and 4-carboxyphenyl radical especially preferably.

[0076] As "an aryl group which may be permuted" in the case of being the aryl group by which R1 may be permuted Preferably A phenyl group, 4-methoxypheny radical, 4-fluoro phenyl group, 4-carboxyphenyl radical, 4-ethoxycarbonyl phenyl group, 2, 4-dimethoxy phenyl group, 2, 5-dimethoxy phenyl group, a 3-carboxy-4-methoxypheny radical, A 4-methoxy-3-methoxycarbonyl phenyl group, a 4-methoxy-3-(methyl carbamoyl) phenyl group, A 3-(dimethyl carbamoyl)-4-methoxypheny radical, a 4-methoxy-3-(1-pyrrolidinyl carbonyl) phenyl group, It is a 4-methoxy-3-(morpholino carbonyl) phenyl group, and is a 4-methoxy-3-methoxycarbonyl phenyl group especially preferably.

[0077] Considering the heteroatom chosen from R or the nitrogen atom in R1, an oxygen atom, and a sulfur atom as a "hetero aryl group" of the hetero aryl group of 1 5 which it has three pieces and which may be permuted thru/or 6 members, it is an oxazolyl radical, a thiazolyl radical, an imidazolyl radical, and a pyridyl radical preferably, and they are an oxazolyl radical and a thiazolyl radical especially preferably.

[0078] It means that the heteroatom chosen from R or the nitrogen atom in R1, an oxygen atom, and a sulfur atom may be preferably permuted by 1 thru/or three substituents as the hetero aryl group of 1 5 which it has three pieces and which may be permuted thru/or 6 members "being permuted", and means that you may permute by 1 thru/or two substituents preferably especially.

[0079] The heteroatom chosen from R or the nitrogen atom in R1, an oxygen atom, and a sulfur atom as a "substituent" of the hetero aryl group of 1 5 which it has three pieces and which may be permuted thru/or 6 members Even if the above-mentioned is permuted preferably Good C1-4 alkyl group; even if the above-mentioned is permuted Good C1-4 alkoxy-group; above-mentioned C1-4 alkylthio-group; -- above-mentioned C1-4 alkyl sulfinyl group; -- above-mentioned C1-4 alkyl sulfonyl group; -- alkyl sulfonyl group; -- above-mentioned halogen atom; -- nitro group; -- cyano group; -- carboxyl group; -- above-mentioned C2-5 alkoxy carbonyl group; -NR three R4 (here) as R3 and R4 being defined by above-mentioned claim 2 -- it is -- amino-group;-N(R5) CONR three R4 (it is here) shown as R3, R4, and R5 being defined by above-mentioned claim 2 -- it is -- ureido radical;-N(R5) COR6 (it is here) shown as R5 and R6 being defined by above-mentioned claim 2 -- it is -- acylamino radical;-CONR three R4 (it is here) shown as R3 and R4 being defined by above-mentioned claim 2 -- it is -- it is the

carbamoyl group shown and is C1-4 alkoxy-group; halogen atom; nitro group; cyano group; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 especially preferably. More specifically, they are a methoxy group, a fluorine atom, a bromine atom, a nitro group, a cyano group, a carboxyl group, a methoxycarbonyl group, an ethoxycarbonyl radical, a methyl carbamoyl group, a dimethyl carbamoyl group, a pyrrolidinyl carbonyl group, and a morpholino carbonyl radical.
[0080] As a "halogen atom" in X, it is a bromine atom and a chlorine atom preferably, and is a bromine atom especially preferably.
[0081] As "C1-4 alkyl group" in R2, it is a methyl group and an ethyl group preferably, and is a methyl group especially preferably.
[0082] As R2, it is a hydrogen atom especially preferably.
[0083] As "C1-4 alkyl group" in R3 and R4, it is a methyl group and an ethyl group preferably, and is a methyl group especially preferably.
[0084] As "a heterocycle radical of 5 which may contain the heteroatom which becomes together with the nitrogen atom which R3 and R4 combine, and is further chosen from a nitrogen atom, an oxygen atom, and a sulfur atom thru/or 6 members" in R3 and R4, it is a pyrrolidinyl radical, a morpholino radical, a piperazinyl radical, and a piperidyl radical preferably, and they are a pyrrolidinyl radical and a morpholino radical especially preferably.
[0085] As "C1-4 alkyl group" in R5, it is a methyl group and an ethyl group preferably, and is a methyl group especially preferably.
[0086] As "C1-4 alkyl group" in R6, it is a methyl group and an ethyl group preferably, and is a methyl group especially preferably.
[0087] As "C1-4 alkoxy group" in R6, it is a methoxy group and an ethoxy radical preferably, and is a methoxy group especially preferably.
[0088] Although "the salt which can be permitted on a remedy" may be what kind of thing as long as it forms the compound shown by the above-mentioned general formula [I], and an avirulent salt for example, hydrochloride; -- hydrobromate; -- hydroiodic-acid salt; -- sulfate; -- nitrate; -- phosphate; -- carbonate; -- hydrogencarbonate; -- inorganic-acid salts, such as a perchlorate, -- Formate; Acetate; Trifluoroacetic acid salt; Propionate; Oxalate; Glycolic-acid salt; Succinate; Lactate; Maleate; hydroxy maleate; -- methyl-maleic-acid salt; -- fumarate; -- adipate; -- tartrate; -- malate; -- citrate; -- benzoate; -- cinnamate; -- ascorbic-acid salt; -- salicylate; -- 2-acetoxy benzoate; -- nicotinic-acid salt; -- organic-acid salts, such as an isonicotinic-acid salt, -- methansulfonic acid salt; -- ethane-sulfonic-acid salt; -- isethionic acid salt; -- benzenesulfonic acid salt; -- p-toluenesulfonic-acid salt; -- sulfonates, such as a naphthalene sulfonate, -- Aspartic-acid salt; Alkali-metal salts, such as acidic-amino-acid salts, such as glutamate, and sodium salt; potassium salt, Magnesium salt; Alkaline-earth-metal salts, such as a calcium salt, ammonium salt, trimethylamine salt; -- triethylamine salt; -- pyridine salt; -- picoline salt; -- dicyclohexylamine salt; -- amino acid salts, such as organic base salts, such as an N and N'-dibenzyl ethylenediamine salt, and a lysine salt; arginine salt, etc. can be mentioned. Moreover, depending on the case, you may be solvate with a hydrate or alcohol.
[0089] As X, a bromine atom has [a 4-methoxy-3-methoxycarbonyl phenyl group] the sulfur atom most desirable [a sulfur atom has / a phenyl group or 4-carboxyphenyl radical / the bromine atom most desirable as R if it states more concretely, when R1 will be a hydrogen atom in the above-mentioned general formula [I] and as Y as X, and] as R1 when R is a hydrogen atom as Y.
[0090] Here, it is included by this invention also about the prodrug compound of the compound shown by the above-mentioned general formula [I], and its metabolite.
[0091] this invention compound is expected as prevention or the remedy of the diabetes mellitus new type which has PTP1B inhibitory action, improves an operation of an insulin directly, and improves insulin susceptibility, insulin resistance, and/or glucose tolerance and which is not until now.
[0092] In using the salt which can be permitted on this invention compound shown by the above-mentioned general formula [I], or its remedy as remedy pharmaceutical preparation Usually, the support well-known in itself permitted in pharmacology, an excipient, a diluent, An extending agent, disintegrator, a stabilizer, a preservative, a buffer, an emulsifier, an aromatic, a coloring agent, On a

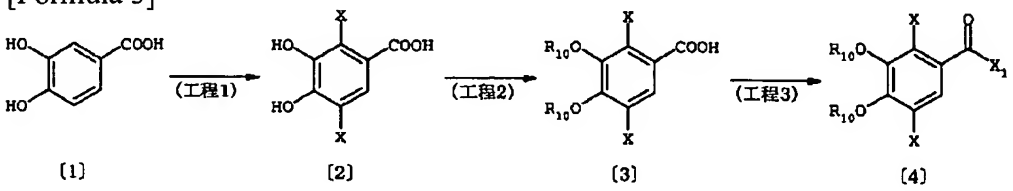
sweetening agent, a viscous agent, corrigent, a solubilizing agent, other additives, and a concrete target, water, Vegetable oil, ethanol or alcohol like benzyl alcohol, a polyethylene glycol, Carbohydrates, such as glycerol thoria ZETETO gelatin, a lactose, and starch, It is mixing with magnesium stearate, talc, lanolin, vaseline, etc. A tablet, Taking orally or a parenteral target can be medicated according to gestalten, such as a pill, powder, a granule, suppositories, injections, ophthalmic solutions, liquids and solutions, a capsule, the trochiscus, an air SOL agent, elixirs, suspension, an emulsion, and syrups. Moreover, this invention compound is usable also as a remedy for animals as well as the activity as a remedy for men.

[0093] Although a dose may change to the class of disease and extent, and the compound list prescribed for the patient with a route of administration, a patient's age, sex, weight, etc., in internal use, it is desirable to usually prescribe especially 1-1000mg 50mg - 800mg for the patient for the compound expressed with the general formula [I] of the adult 1 sunny above-mentioned.

[0094] Next, although the manufacture approach of this invention compound expressed with the above-mentioned general formula [I] is described concretely, the manufacture approach of this invention compound of it not being what is limited to these is natural.

[0095]

[Formula 3]



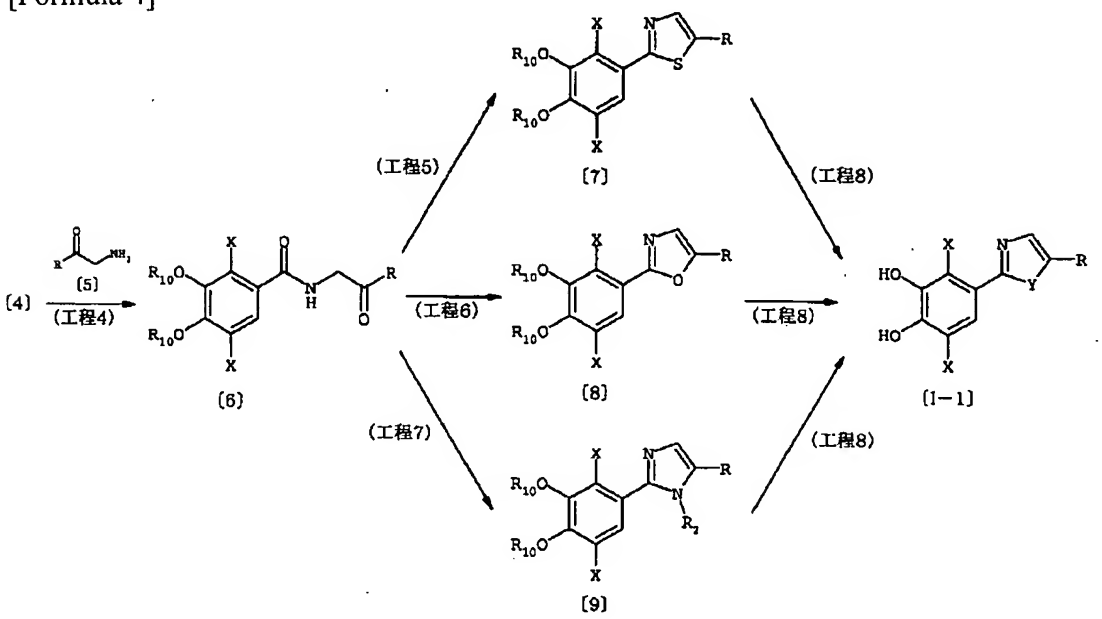
[0096] In addition, R10 in the above-mentioned formula is hydroxyl-group protective groups, such as an acetyl group, a propionyl radical, benzyl, a trimethylsilyl radical, and a methyl group, X1 is a halogen atom, and X is as defining above.

(Process 1) a compound [2] -- a compound [1] -- warming the inside of a solvent, and under cooling -- it is compoundable by making it react with a halogenating agent in the bottom. As a desirable halogenating agent, a bromine, chlorine, N-BUROMO succinimid, a sulfuryl chloride, N-chloro succinimid, tert-butoxy chloride, etc. are mentioned. As a desirable solvent, an organic solvent or water, such as halogen system solvent; benzene, such as polar-solvent; dichloromethanes [, such as alcoholic solvent; dimethylformamide], such as ether system solvent; methanols, such as dioxane and a tetrahydrofuran, and ethanol, and chloroform, and toluene, may be mentioned, and you may be these mixed solvents. [, such as a hydrocarbon system solvent; acetic acid,]

[0097] (Process 2) a compound [3] -- a compound [2] -- the bottom of base existence, an acetic anhydride, a propionic anhydride, benzyl chloride, a benzyl star's picture, trimethylsilyl chloride, a methyl iodide, etc. -- or the bottom of acid existence, an acetic anhydride, a propionic anhydride, etc. and warming the inside of a solvent or a non-solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable base, organic bases, such as a pyridine, triethylamine, N-methyl morpholine, and N-methyl piperidine, are mentioned. As a desirable solvent, an organic solvent or water, such as the hydrocarbon system solvent; ether, such as halogen system solvent; benzene, such as dichloromethane and chloroform, toluene, and a hexane, a tetrahydrofuran, dioxane, diisopropyl ether, and diethoxy ethane, may be mentioned, and you may be these mixed solvents. [, such as an ether system solvent; acetic acid,]

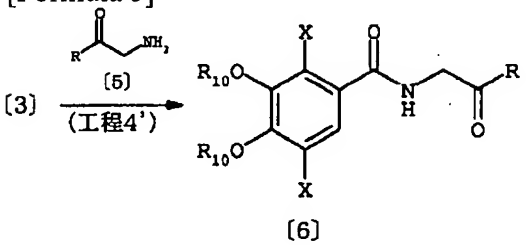
[0098] (Process 3) a compound [4] -- a compound [3] -- warming the inside of a solvent, and under cooling -- it is compoundable by making it react with an acid halide-ized agent in the bottom. As a desirable acid halide-ized agent, an oxalyl chloride, a thionyl chloride, a phosphorus trichloride, a phosphorus pentachloride, phosphorus oxychloride, etc. are mentioned. As a desirable solvent, organic solvents [, such as halogen system solvent; dimethylformamide /, such as hydrocarbon system solvents such as polar-solvent; toluene,], such as chloroform and dichloromethane, may be mentioned, and you

may be these mixed solvents. Thus, the compound expressed with a general formula [I] is compoundable by making the obtained compound [4] react according to the approach shown below.
[0099]
[Formula 4]

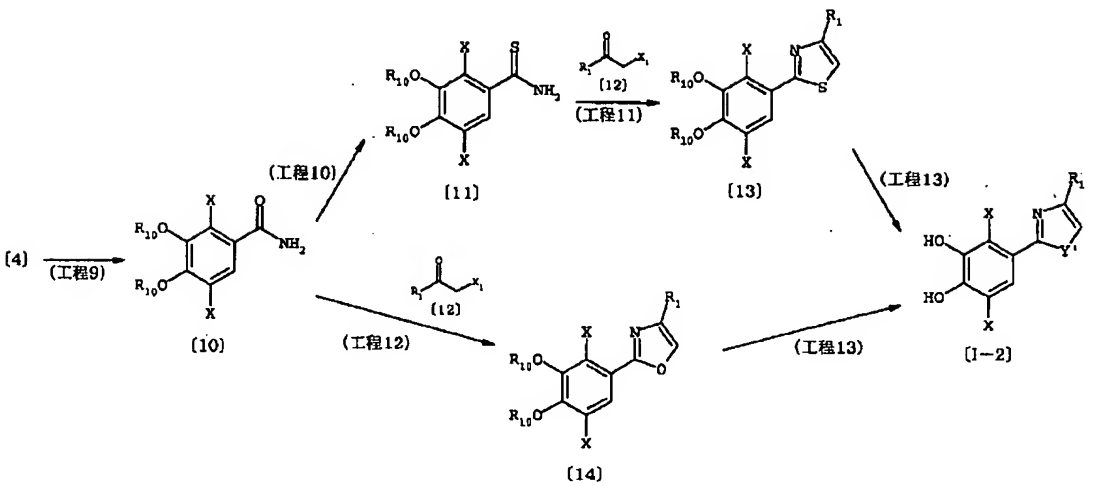


[0100] In addition, R, R2, R10, X, X1, and Y in the above-mentioned formula are as defining above. (Process 4) a compound [6] -- a compound [4] and a compound [5] -- warming the bottom of base existence, the inside of a solvent or a non-solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable base, organic bases, such as inorganic base; triethylamines, such as sodium acetate, a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, and a sodium hydrogencarbonate, and a pyridine, are mentioned. As a desirable solvent, an organic solvent or water, such as ester solvent; chloroform [, such as polar-solvent; toluene /, such as hydrocarbon system solvent; ethyl acetate,], such as ether system solvent; acetonitriles, such as a tetrahydrofuran, dioxane, dimethoxyethane, the ether, and diisopropyl ether, and dimethylformamide, and dichloromethane, is mentioned, and you may suit with these mixed solvents. [, such as a halogen system solvent,]
[0101] (Process 5) the process in which this process forms a thiazole ring in case Y is a sulfur atom -- it is -- namely, a compound [7] -- a compound [6] -- warming the inside of a solvent, and under cooling -- it is compoundable by making it react with a thiocarbonyl-ized agent in the bottom. As a desirable thiocarbonyl-ized agent, it is 5 sulfuration 2 Lynn, 2, and 4-screw. - (4-methoxypheny) -1, 3-dithia -2, 4-JIHOSUFETAN -2, 4-disulfide, 2, the 4-dimethyl -1, 3-dithia -2, 4-JIHOSUFETAN -2, 4-disulfide, etc. are mentioned. As a desirable solvent, organic solvents, such as polar solvents [, such as a hydrocarbon system solvent; acetonitrile,], such as ether system solvent; toluene, such as halogen system solvent; tetrahydrofurans, such as chloroform and dichloromethane, and dimethoxyethane, and a xylene, may be mentioned, and you may be these mixed solvents.
[0102] (Process 6) the process in which this process forms an oxazole ring in case Y is an oxygen atom -- it is -- namely, a compound [8] -- a compound [6] -- warming the bottom of dehydration-ized agent existence, the inside of a solvent or a non-solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable dehydration-ized agent, 3 phosphoryl chlorides, a thionyl chloride, diphosphorus pentaoxide, etc. are mentioned. As a desirable solvent, hydrocarbon system solvents [, such as halogen system solvent; toluene,], such as chloroform, may be mentioned, and you may be these mixed solvents.
[0103] (Process 7) compound R2NH2 to which this process is a process which forms an imidazole ring in case Y is -NR2- (it is here and R2 is as defining as above-mentioned claim 1), namely, a compound

[9] corresponds with a compound [6] -- warming the inside of a solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable solvent, it is an acetic acid etc.
[0104] This process is a process for being desorbed from the protective group of the hydroxyl-group protective group introduced in the above-mentioned process 2, or/and the carboxyl group protected beforehand. (Process 8) Although it will not be limited especially if it is the approach used, for example usually, a compound [I-1] the compound [7], compound [8], or compound [9] obtained at the above-mentioned process 5, the process 6, or the process 7 -- warming the bottom of base existence or acid existence, the inside of a solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable base, inorganic bases, such as organic base; sodium hydroxides, such as ammonia, and potassium carbonate, are mentioned. As a desirable acid, a hydrochloric acid, a hydrobromic acid, a sulfuric acid, etc. are mentioned. As a desirable solvent, an organic solvent or water, such as a methanol and ethanol, may be mentioned, and you may be these mixed solvents. [, such as an alcoholic solvent; tetrahydrofuran,] [, such as an ether system solvent; acetic acid,] In addition, the above-mentioned process 1 thru/or the process 8 are effective especially when R1 in the above-mentioned general formula [I] is a hydrogen atom. Here, a compound [6] is compoundable also by the approach shown below.
[0105]
[Formula 5]

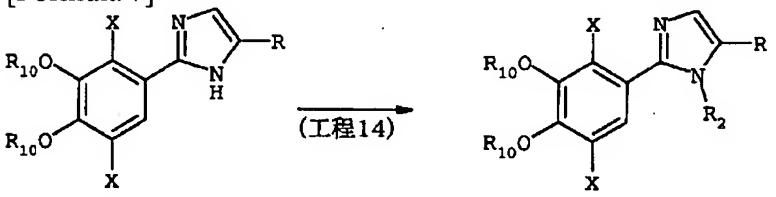


[0106] In addition, R, R10, and X in the above-mentioned formula are as defining above.
(Process 4') a compound [6] -- a compound [3] and a compound [5] -- a condensing agent -- the need -- responding -- warming the bottom of activator existence, the inside of a solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable condensing agent, a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and a hydrochloride, dicyclohexylcarbodiimide, diphenyl phosphoryl azide, carbonyldiimidazole, etc. are mentioned. As a desirable activator, 1-hydroxy benzotriazol, hydroxysuccinimide, N-hydroxy-5-norbornene -2, 3-dicarboxylic acid imide, etc. are mentioned. As a desirable solvent, organic solvents [, such as a halogen system solvent; tetrahydrofuran, /, such as hydrocarbon system solvents such as ether system solvent; toluene,], such as polar-solvent; chloroform, such as dimethylformamide and an acetonitrile, and dichloromethane, may be mentioned, and you may be these mixed solvents. Moreover, the compound expressed with a general formula [I] is compoundable also by making the compound [4] compounded as mentioned above react according to the approach shown below.
[0107]
[Formula 6]



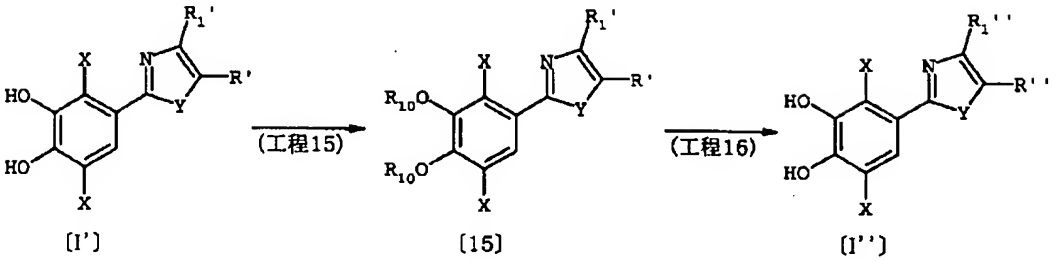
[0108] In addition, Y' in the above-mentioned formula is a sulfur atom and an oxygen atom, and R1, R10, X, and X1 are as defining above.
(Process 9) a compound [10] -- a compound [4] and ammonia -- warming the inside of a solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable solvent, an organic solvent or water, such as ester solvent, such as chloroform and dichloromethane, may be mentioned, and you may be these mixed solvents. [, such as halogen system solvent; toluene,] [, such as a hydrocarbon system solvent; tetrahydrofuran,] [, such as ether system solvent; ethyl acetate,]
[0109] (Process 10) the process in which this process forms a thiazole ring in case Y is a sulfur atom -- it is -- namely, a compound [11] -- a compound [10] -- warming the inside of a solvent, and under cooling -- it is compoundable by making it react with a thiocarbonyl-ized agent in the bottom. As a desirable thiocarbonyl-ized agent, it is phosphorus-pentasulfide, 2, and 4-screw. - (4-methoxypheny) -1, 3-dithia - 2, 4-JIHOSUFETAN -2, 4-disulfide, 2, the 4-dimethyl -1, 3-dithia -2, 4-JIHOSUFETAN -2, 4-disulfide, etc. are mentioned. As a desirable solvent, organic solvents, such as polar solvents [, such as a hydrocarbon system solvent; acetonitrile,], such as ether system solvent; toluene, such as halogen system solvent; tetrahydrofurans, such as chloroform and dichloromethane, and dimethoxyethane, and a xylene, may be mentioned, and you may be these mixed solvents.
[0110] (Process 11) a compound [13] -- a compound [11] and a compound [12] -- warming the bottom of base existence or nonexistence, the inside of a solvent or a non-solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable base, organic bases, such as inorganic base; triethylamines, such as sodium acetate, a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, and a sodium hydrogencarbonate, and a pyridine, are mentioned. As a desirable solvent, organic solvents, such as halogen system solvents, such as ester solvent; chloroform [, such as polar-solvent; toluene /, such as hydrocarbon system solvent; ethyl acetate], such as ether system solvent; acetonitriles, such as alcoholic solvent; tetrahydrofurans, such as a methanol, ethanol, and isopropyl alcohol, dioxane, dimethoxyethane, the ether, and diisopropyl ether, and dimethylformamide, and dichloromethane, are mentioned, and you may suit with these mixed solvents.
[0111] (Process 12) the process in which this process forms an oxazole ring in case Y is an oxygen atom -- it is -- namely, a compound [14] -- a compound [10] and a compound [12] -- warming the bottom of base existence or nonexistence, the inside of a solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable base, organic bases, such as inorganic base; triethylamines, such as sodium acetate, a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, and a sodium hydrogencarbonate, and a pyridine, are mentioned. As a desirable solvent, organic solvents, such as halogen system solvents, such as ester solvent; chloroform [, such as polar-solvent; toluene /, such as hydrocarbon system solvent; ethyl acetate], such as ether system solvent; acetonitriles, such as alcoholic solvent; tetrahydrofurans, such as a methanol, ethanol, and isopropyl alcohol, dioxane, dimethoxyethane, the ether, and diisopropyl ether, and dimethylformamide, and

dichloromethane, are mentioned, and you may suit with these mixed solvents.
[0112] This process is a process for being desorbed from the protective group of the hydroxyl-group protective group introduced in the above-mentioned process 2, or/and the carboxyl group protected beforehand. (Process 13) usually, the compound [13] or compound [14] with which the compound [I-2] was obtained at the above-mentioned process 11 or the process 12, for example although it was not limited especially when it was the approach used -- warming the bottom of base existence or acid existence, the inside of a solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable base, inorganic bases, such as organic base; sodium hydroxides, such as ammonia, and potassium carbonate, are mentioned. As a desirable acid, a hydrochloric acid, a hydrobromic acid, a sulfuric acid, etc. are mentioned. As a desirable solvent, an organic solvent or water, such as a methanol and ethanol, may be mentioned, and you may be these mixed solvents. [, such as an alcoholic solvent; tetrahydrofuran,] [, such as an ether system solvent; acetic acid,] In addition, the above-mentioned process 9 thru/or the process 13 are effective especially when R in the above-mentioned general formula [I] is a hydrogen atom. Here, in the case of the compound expressed with the above-mentioned general formula [I] whose R2 is C1-4 alkyl group, R2 can also compound a compound [9] for the compound [9'] which is a hydrogen atom after composition according to the following process 14 according to a process 7 beforehand.
[0113]
[Formula 7]



[9'] [9]

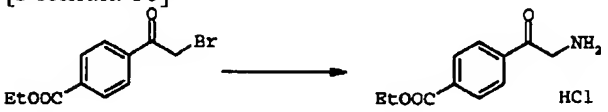
[0114] In addition, R, R2, R10, and X in the above-mentioned formula are as defining above. (Process 14) a compound [9] -- a compound [9'] and compound R2-X1 (it is here and R2 and X1 are as defining above) -- warming the bottom of base existence, the inside of a solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable base, organic bases, such as inorganic base; triethylamines, such as sodium acetate, a sodium carbonate, potassium carbonate, a sodium hydroxide, a potassium hydroxide, and a sodium hydrogencarbonate, and a pyridine, are mentioned. As a desirable solvent, organic solvents, such as halogen system solvents, such as ester solvent; chloroform [, such as polar-solvent; toluene /, such as hydrocarbon system solvent; ethyl acetate], such as ether system solvent; acetonitriles, such as alcoholic solvent; tetrahydrofurans, such as a methanol and ethanol, dioxane, dimethoxyethane, the ether, and diisopropyl ether, and dimethylformamide, and dichloromethane, may be mentioned, and you may be these mixed solvents. In addition, in this process, the mixture of the compound whose R1 is a hydrogen atom, and the compound whose R is a hydrogen atom may be obtained, and each can be isolated according to the usual isolation approach in that case.
[0115] Furthermore, when R in the above-mentioned general formula [I] or one side of R1 is the aryl group which has at least one -CONR three R4 (here, R3 and R4 are as defining as above-mentioned claim 2), it can compound by performing a following process 15 thru/or a following process 16 after compounding the compound of the general formula [I] which has a corresponding carboxyl group.
[0116]
[Formula 8]



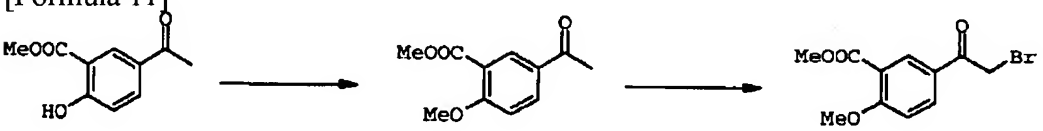
[I'] [15] [I'']

[0117] In addition, either R' in the above-mentioned formula or R1' is a hydrogen atom, and another side is an aryl group which has at least one carboxyl group. One side of R"or R1" is a hydrogen atom, another side is at least one -CONR three R4 (it is here and R3 and R4 are as defining as above-mentioned claim 2), and X, Y, and R10 are as defining above.
(Process 15) a compound [15] -- a compound [I'] -- the bottom of base existence, an acetic anhydride, a propionic anhydride, benzyl chloride, a benzyl star's picture, trimethylsilyl chloride, a methyl iodide, etc. -- or the bottom of acid existence, an acetic anhydride, a propionic anhydride, etc. and warming the inside of a solvent or a non-solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable base, organic bases, such as a pyridine, triethylamine, N-methyl morpholine, and N-methylpyridine, are mentioned. As a desirable solvent, an organic solvent or water, such as the hydrocarbon system solvent; ether, such as halogen system solvent; benzene, such as dichloromethane and chloroform, toluene, and a hexane, a tetrahydrofuran, dioxane, diisopropyl ether, and diethoxy ethane, may be mentioned, and you may be these mixed solvents. [, such as an ether system solvent; acetic acid,]
[0118] (Process 16) a compound [I"] -- a compound [15] and a compound NHR three R4 -- a condensing agent -- the need -- responding -- warming the bottom of activator existence, the inside of a solvent, and under cooling -- it is compoundable by making it react in the bottom. As a desirable condensing agent, a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and a hydrochloride, dicyclohexylcarbodiimide, diphenyl phosphoryl azide, carbonyldiimidazole, etc. are mentioned. As a desirable activator, 1-hydroxy benzotriazol, hydroxysuccinimide, N-hydroxy-5-norbornene -2, 3-dicarboxylic acid imide, etc. are mentioned. As a desirable solvent, organic solvents [, such as a halogen system solvent; tetrahydrofuran, /, such as hydrocarbon system solvents such as ether system solvent; toluene,], such as polar-solvent; chloroform, such as dimethylformamide, dimethyl sulfoxide, and an acetonitrile, and dichloromethane, may be mentioned, and you may be these mixed solvents. In addition, in these above-mentioned process 1 thru/or each process of 16, each process may be performed, when protective groups, such as a hydroxyl-group protective group, **** before end product composition, for example, after performing the same reaction as the above-mentioned process 2 and reintroducing a protective group.
[0119] Thus, isolation purification of the compound expressed with the obtained above-mentioned general formula [I] can be carried out with a well-known separation purification means, for example, concentration, vacuum concentration, solvent extraction, crystallization, recrystallization, or a chromatography.
[0120] The prodrug compound of the compound expressed with the above-mentioned general formula [I] by the compound of this invention, a hydrate, or solvate with the organic solvent permitted pharmacologically is also contained in this invention.
[Embodiment of the Invention]
[0121] Next, although the example of manufacture, an example, and the example of a trial are given and this invention is explained concretely, this invention is not limited to this at all.
[Example]
[0122] Composition of example of manufacture 14-(2-BUROMO acetyl) ethyl benzoate [0123]
[Formula 9]

[0124] 25% of hydrogen bromide-acetic-acid solution (10microl) was added to the acetic-acid (30ml) solution of 4-acetyl ethyl benzoate (6.0g), and it stirred for 30 minutes among the room temperature. The bromine (1.69ml) was dropped at this solution in 4 steps among the room temperature, and it stirred for 30 minutes. Water (30ml) was added after stirring and it stirred for further 1 hour. The obtained crystal was separated and the heading compound (7.3g, 86% of yield) of white gray powder was obtained by carrying out reduced pressure drying after washing by water (30ml) and the hexane (30ml).
[0125] Composition of example of manufacture 24-(2-amino acetyl) ethyl benzoate, and a hydrochloride
[0126]
[Formula 10]

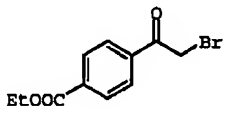
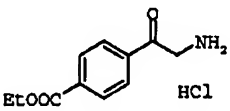
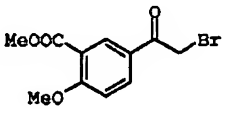


[0127] The compound (7.0g) and sodium which were obtained in the above-mentioned example 1 of manufacture under the argon ambient atmosphere The acetonitrile (35ml) solution of a diformyl amide (2.95g) was stirred among the room temperature all night. After stirring, temperature up of this solution was carried out to 70 degrees C, and it was filtered at the time of heat. After adding ethanol (77ml) to the obtained residue and dropping concentrated hydrochloric acid (7.7ml), heating reflux was carried out for 1 hour. After removing the solvent and performing toluene (10ml) azeotropy twice, ethyl acetate (35ml) was added and it stirred among the room temperature for 1 hour. After it separated the depositing crystal and ethyl acetate (14ml) washed, the heading compound (3.7g, 59% of yield) of white powder was obtained by carrying out reduced pressure drying.
[0128] Composition of example of manufacture 33-(2-BUROMO acetyl)-6-methoxy methyl benzoate
[0129]
[Formula 11]



[0130] 1) 3-acetyl - The sodium hydride (1.36g) of mineral-oil suspension was added to the dimethylformamide (60ml) solution of 6-methoxy methyl benzoate 3-acetyl-6-hydroxybenzoic-acid methyl (6.00g) 60%, and it stirred for 30 minutes among the room temperature. This reaction mixture was ice-cooled after stirring, the methyl iodide (3.84ml) was added, and it stirred for three more days in the room temperature. After adding 1-N hydrochloric acid (5ml) and water (120ml) to this reaction mixture, the heading compound (4.63g, 72% of yield) was obtained by separating the depositing crystal.
[0131] 2) 25% of hydrogen bromide-acetic-acid solution 1 ** was added to the acetic-acid (10ml) solution of the compound (2.00g) obtained by the 3-(2-BUROMO acetyl)-6-methoxy methyl benzoate above 1, and the bromine (0.49ml) was dropped at it. After stirring in a room temperature for 1 hour, the heading compound (2.54g, 92% of yield) was obtained by separating the crystal which added water and deposited. As mentioned above, the compound obtained in the example 1 of these manufactures thru/or the example 3 of manufacture is shown in the following table 1.
[0132]
[A table 1]

表 1

製造例	化合物	^1H NMR (δ) ppm
1		$CDCl_3$ 300 MHz 1.42 (3H, t, J=7.0Hz) 4.42 (2H, q, J=7.0Hz) 4.47 (2H, s) 8.04 (2H, d, J=8.1Hz) 8.15 (2H, d, J=8.1Hz)
2		DMSO-d_6 400 MHz 1.35 (3H, t, J=7.0Hz) 4.37 (2H, q, J=7.0Hz) 4.64 (2H, s) 8.12 (2H, d, J=8.1Hz) 8.14 (2H, d, J=8.1Hz) 8.42 (3H, br)
3		$CDCl_3$ 300 MHz 3.93 (3H, s) 4.00 (3H, s) 4.42 (2H, s) 7.05 (1H, d, J=8.8Hz) 8.15 (1H, dd, J=2.6, 8.8Hz) 8.55 (1H, d, J=2.6Hz)

[0133] Composition of an example 12-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl thiazole ([Compound I]:R= phenyl, an R1= hydrogen atom, X= bromine atom, Y= sulfur atom)
Process 1 2, 5-dibromo-3,4-dihydroxybenzoic acid (compound [2])
The bromine (24.1ml) was dropped at the acetic-acid (300ml) solution of 3,4-dihydroxybenzoic acid (30g), and it stirred at 50 degrees C for 24 hours. The bromine (12ml) was further added to this reaction mixture after stirring, and it stirred at 50 degrees C for 18 hours. After cooling reaction mixture, separating the depositing crystal and an acetic acid's washing, the heading compound (11.1g, 18.3% of yield) was obtained by drying.
[0134] Process 2 3, 4-diacetoxy -2, 5-dibromo benzoic acid (compound [3])
The acetic anhydride (16.8ml) was added to the pyridine (34ml) solution of the compound (11.1g) obtained at the above-mentioned process 1, and it stirred among the room temperature for 20 hours. After distilling off the solvent and adding dilute hydrochloric acid, the depositing crystal was separated and it washed with water. The heading compound (13.0g, 92% of yield) was obtained by drying the obtained crystal.
[0135] Process 3 3, 4-diacetoxy -2, 5-dibromobenzoyl chloride (compound [4])
A thionyl chloride (0.111ml) and dimethylformamide (1 **) were added to the toluene (2ml) suspension of the compound (200mg) obtained at the above-mentioned process 2 one by one, and it stirred at 50 degrees C for 1 hour. The solvent and the superfluous thionyl chloride were distilled off after stirring, and the heading compound of a rough product was obtained by carrying out azeotropy with toluene.
[0136] Process 4 N-(benzoyl methyl)-3, 4-diacetoxy -2, 5-dibromo benzamide (compound [6])
2-amino acetophenone and the hydrochloride (87mg) were added to the ethyl-acetate (2ml) solution of the rough product obtained at the above-mentioned process 3, and, subsequently the sodium acetate water solution (2.53 mols / 1.2ml) was dropped at it under ice-cooling stirring. After stirring for 30 minutes under this temperature, liquids were separated and sequential washing of the organic layer was carried out with 1-N hydrochloric acid, saturation sodium bicarbonate water, water, and saturation brine. After drying with magnesium sulfate, the heading compound which is a rough product of brown oily matter was obtained by distilling off a solvent.
[0137] Process 5 2-(3, 4-diacetoxy -2, 5-dibromo phenyl)-5-phenyl thiazole (compound [7])
To the rough product obtained at the above-mentioned process 4, it is 2 and 4-screw. - (4-methoxypheny) -1, 3-dithia -2, 4-JIHOSUFETAN -2, 4-disulfide (162mg), and chloroform (2ml) were added one by one, and heating reflux was carried out for 2.5 hours. After cooling to a room temperature, silica gel thin-layer chromatography (expansion solvent; 25% ethyl acetate / chloroform) refined reaction mixture, and the rough crystal was obtained. The heating reflux of the ethyl-acetate (2ml)

suspension of a rough crystal was carried out, and the heading compound (159mg, 62% of yield) was obtained by separating the crystal which added the hexane (4ml) after radiationnal cooling, and deposited.

[0138] Process 8 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl thiazole (compound [I])

The saturated ammonia methanol (1ml) was added to the compound (85mg) obtained at the above-mentioned process 5, and it stirred among the room temperature for 1 hour. After distilling off a solvent, water was added and the heading compound (69mg, 97% of yield) was obtained by separating the crystal which made it acidity and deposited with dilute hydrochloric acid.

[0139] Composition of an example 25-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole ([Compound I]:R=4-carboxyphenyl, an R1= hydrogen atom, X= bromine atom, Y= sulfur atom)

Process 3 3, 4-diacetoxy -2, 5-dibromobenzoyl chloride (compound [4])

A thionyl chloride (2.21ml) and dimethylformamide (0.2ml) were added to the toluene (40ml) suspension of the compound (4.0g) obtained at the process 2 of the above-mentioned example 1 one by one under the nitrogen air current, and it stirred at 50 degrees C for 1 hour. After distilling off the solvent and the superfluous thionyl chloride and boiling two times with toluene (10ml), the heading compound of a rough product was obtained by carrying out reduced pressure drying.

[0140] Process 4 N-[(4-ethoxycarbonyl benzoyl) methyl]-3, 4-diacetoxy -2, 5-dibromo benzamide (compound [6])

The ethyl-acetate (40ml) suspension of the 4-(2-amino acetyl) ethyl benzoate and the hydrochloride (2.46g) obtained in the above-mentioned example 2 of manufacture was added to the rough product obtained at the above-mentioned process 3, and, subsequently the sodium acetate water solution (2.53 mols / 40ml) was dropped at it under ice-cooling stirring. After stirring in a room temperature for 2 hours, double sampling was carried out with ethyl acetate (20ml), and saturation brine (40ml) washed the organic layer. After drying with a sodium sulfate, the heading compound which is a rough product of brown oily matter was obtained by distilling off a solvent.

[0141] Process 5 2-(3, 4-diacetoxy -2, 5-dibromo phenyl)-5-(4-ethoxycarbonyl phenyl) thiazole (compound [7])

To the rough product obtained at the above-mentioned process 4, it is 2 and 4-screw. - (4-methoxypheny) -1, 3-dithia -2, 4-JIHOSUFETAN -2, 4-disulfide (2.90g), and a tetrahydrofuran (40ml) were added one by one, and heating reflux was carried out for 2 hours. After cooling to a room temperature, saturation sodium bicarbonate water (40ml) was added, and it stirred for 30 minutes. The crystal which added water and deposited was separated and water (10ml) and 50% methanol water (10ml) washed. The heading compound (2.06g, 35% of yield) of a **** yellow crystal was obtained by refining the obtained residue after reduced pressure drying with a silica gel column chromatography (expansion solvent; 25% ethyl acetate / chloroform).

[0142] Process 8 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-carboxyphenyl) thiazole (compound [I])

1-N sodium-hydroxide water solution (8.23ml) was dropped at the methanol (8.23ml) solution of the compound (800mg) obtained at the above-mentioned process 5 under ice-cooling stirring under the nitrogen air current, subsequently the tetrahydrofuran (4.23ml) was added, and it stirred at 50 degrees C for 1 hour. After distilling off the solvent and carrying out azeotropy with toluene, water was added, it was made pH1 thru/or 2 with 2-N hydrochloric acid, and stirring crystallization was performed among the room temperature. After separating the depositing crystal and washing with water (5ml), the heading compound (529mg, 82% of yield) of a black crystal was obtained by carrying out reduced pressure drying.

[0143] The compound of a publication was obtained to a table 1 thru/or a table 5 like the example 3 the example 1 of the example 18 above-mentioned thru/or the example 2.

[0144] Composition of an example 192-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole (a [Compound I]:R= hydrogen atom, R1=4-methoxy-3-methoxycarbonyl phenyl, X= bromine atom, Y= sulfur atom)

Process 3 3, 4-diacetoxy -2, 5-dibromobenzoyl chloride (compound [4])

A thionyl chloride (1.66ml) and dimethylformamide (0.15ml) were added to the toluene (30ml) suspension of the compound (3.00g) obtained at the process 2 of the above-mentioned example 1 one by one, and it stirred at 50 degrees C for 1 hour. The heading compound of a rough product was obtained by distilling off a solvent after stirring.

[0145] Process 9 3, 4-diacetoxy -2, 5-dibromo benzamide (compound [10])

It dissolved in chloroform (30ml) and the rough product obtained at the above-mentioned process 3 was stirred under the ammonia gas ambient atmosphere for 3 hours. After distilling off a solvent, the pyridine (15ml) was made to suspend, the acetic anhydride (5ml) was added, and it stirred among the room temperature for 15 hours. The solvent was distilled off, water and ethyl acetate were added, and after separating liquids, sequential washing of the organic layer was carried out with 1-N hydrochloric acid, saturation sodium bicarbonate water, water, and saturation brine. The heading compound (2.90g, 97% of yield) was obtained by distilling off a solvent after desiccation with magnesium sulfate.

[0146] Process 10 3, 4-diacetoxy -2, 5-dibromo benzothioamide (compound [11])

The compound (2.90g) obtained at the above-mentioned process 9 and 2, 4-screw - (4-methoxypheny) The heating reflux of the tetrahydrofuran suspension of -1, 3-dithia -2, 4-JIHOSUFETAN -2, and 4-disulfide (2.38g) was carried out for 2 hours, sodium bicarbonate water was added after radiationnal cooling, and ethyl acetate extracted. Sequential washing of the organic layer was carried out with saturation sodium bicarbonate water, water, and saturation brine, and it dried with magnesium sulfate. The heading compound (2.63g, 87.2% of yield) was obtained after distilling off a solvent by refining with a silica gel column chromatography (expansion solvent; chloroform - 5% ethyl-acetate / chloroform - 10% ethyl acetate / chloroform).

[0147] Process 11 2-(3, 4-diacetoxy -2, 5-dibromo phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole (compound [13])

After carrying out the heating reflux of the compound (2.00g) obtained at the above-mentioned process 10, the 3-(2-BUROMO acetyl)-6-methoxy methyl benzoate (1.54g) obtained in the above-mentioned example 3 of manufacture, and the ethanol (20ml) solution of sodium acetate (439mg) for 1.5 hours and distilling off a solvent, it was made to dissolve in a pyridine (8ml), the acetic anhydride (4ml) was added, and it stirred among the room temperature for 3 hours. Dilute hydrochloric acid and chloroform were added after distilling off a solvent, and after separating liquids, sequential washing of the organic layer was carried out with water and saturation brine, and it dried with magnesium sulfate. After distilling off the solvent and making ethanol suspend the depositing rough crystal, the heading compound (1.34g, 63% of yield) was obtained by separating the depositing crystal.

[0148] Process 13 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole (compound [I])

The saturated ammonia methanol (3ml) was added to the methanol (10ml) suspension of the compound (1.00g) obtained at the above-mentioned process 11, and it stirred among the room temperature for 1 hour. After distilling off a solvent, water was added and it was made acidity with dilute hydrochloric acid. The depositing crystal was separated and the heading compound (872mg, 100% of yield) was obtained by washing under chloroform.

[0149] Composition of an example 204-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole (a [Compound I]:R= hydrogen atom, R1=3-carboxy-4-methoxypheny, X= bromine atom, Y= sulfur atom)

Process 13 4-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole (compound [I])

1-N sodium-hydroxide water solution (10ml) was added to the methanol (10ml) and tetrahydrofuran (10ml) mixing suspension of a compound (800mg) which were obtained at the process 11 of the above-mentioned example 19, and it stirred at 40 degrees C for 1 hour. Water was added after distilling off a solvent and 2-N hydrochloric acid (5ml) was added. After separating the depositing crystal and washing with water, the heading compound (639mg, 82% of yield) was obtained by drying.

[0150] example 212-(2, 5-dibromo -3, 4-dihydroxy phenyl)- composition (a [Compound I]:R= hydrogen atom --) of 4-[4-methoxy-3-(methyl carbamoyl) phenyl] thiazole R1=4-methoxy-3-(methyl carbamoyl)

phenyl, X= bromine atom, Y= sulfur atom process 15 4-(3-carboxy-4-methoxypheny)-2-(3, 4-diacetoxy -2, 5-dibromo phenyl) thiazole (compound [15])
The pyridine (2ml) and the acetic anhydride (0.966ml) were added to the compound (639mg) obtained in the above-mentioned example 20, and it stirred among the room temperature for 2 hours. After distilling off a solvent, chloroform and 2-N hydrochloric acid were added and insoluble matter was carried out the ** exception. The organic layer was washed with water, and after drying with magnesium sulfate, the heading compound (527mg, 70% of yield) was obtained by refining the obtained residue with a silica gel column chromatography (ethyl acetate: expansion solvent; chloroform = 1:1).
[0151] Process 162-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(methyl carbamoyl) phenyl] thiazole (compound [I])
The 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, the hydrochloride (72mg), and 1-hydroxy benzotriazol and a hydrate (58mg) were added to the dimethylformamide solution of the compound (200mg) obtained at the above-mentioned process 15, and it stirred among the room temperature for 1 hour. The monomethylamine water solution (0.4ml) was added 40% after stirring, and it stirred among the room temperature for further 1 hour. The depositing crystal was separated, after it added water and 2-N hydrochloric acid neutralized. After carrying out sequential washing under water and chloroform, the heading compound (156mg, 89% of yield) was obtained by drying.
[0152] The compound of a publication was obtained to a table 6 thru/or a table 8 like the example 22 the example 19 of the example 33 above-mentioned thru/or the example 21.
[0153] Composition of example 342-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) oxazole ([Compound I]:R=4-ethoxycarbonyl phenyl, an R1= hydrogen atom, X= bromine atom, Y= oxygen atom)
Process 3 3, 4-diacetoxy -2, 5-dibromobenzoyl chloride (compound [4])
A thionyl chloride (221microl) and dimethylformamide (0.2ml) were added to the toluene (4ml) suspension of the compound (400mg) obtained at the process 2 of the above-mentioned example 1 one by one under the nitrogen air current, and it stirred at 50 degrees C for 2 hours. After distilling off the solvent and the superfluous thionyl chloride and boiling two times with toluene (10ml), the heading compound of a rough product was obtained by carrying out reduced pressure drying.
[0154] Process 4 N-[(4-ethoxycarbonyl benzoyl) methyl]-3, 4-diacetoxy -2, 5-dibromo benzamide (compound [6])
The ethyl-acetate (4ml) suspension of the 4-(2-amino acetyl) ethyl benzoate and the hydrochloride (246mg) obtained in the above-mentioned example 2 of manufacture was added to the rough product obtained at the above-mentioned process 3, and, subsequently the sodium acetate water solution (2.53 mols / 4ml) was dropped at it under ice-cooling stirring. After being under ice-cooling and stirring for 2 hours, double sampling was carried out with ethyl acetate (20ml), and saturation brine (40ml) washed the organic layer. After drying with a sodium sulfate, the heading compound (551mg) which is a rough product of a light yellow crystal was obtained by distilling off a solvent.
[0155] Process 6 2-(3, 4-diacetoxy -2, 5-dibromo phenyl)-5-(4-ethoxycarbonyl phenyl) oxazole (compound [8])
3 phosphoryl chlorides (47.7microl) were added to the chloroform (1.5ml) solution of the rough product (150mg) obtained at the above-mentioned process 4, and heating reflux was carried out for 5 hours. Saturation sodium bicarbonate water (1ml) and water (1ml) were added after radiationnal cooling, it stirred for 30 minutes, and ethyl acetate (5ml) extracted twice. Saturation brine (5ml) washed the organic layer, the solvent was distilled off after desiccation with magnesium sulfate, and the heading compound (74.1mg, 51% of yield) of a **** yellow crystal was obtained by refining with thin-layer chromatography (5% ethyl acetate / chloroform).
[0156] Process 8 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) oxazole (compound [I])
The saturated ammonia methanol solution (1.0ml) and the tetrahydrofuran (1.0ml) were added to the compound (41mg) obtained at the above-mentioned process 6, and it stirred among the room temperature for 1 hour. Azeotropy was carried out with toluene after distilling off a solvent, and water

(2ml) and concentrated hydrochloric acid (2ml) were added one by one. After it separated the depositing crystal and water (4ml) and chloroform (4ml) washed, the heading compound (32.8mg, 97% of yield) of a white crystal was obtained by carrying out reduced pressure drying.

[0157] Composition of example 355-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole ([Compound I]:R=4-carboxyphenyl, an R1= hydrogen atom, X= bromine atom, Y= oxygen atom)

Process 85-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole (compound [I])

After adding a methanol (1ml) and a tetrahydrofuran (1ml) to the compound (29.0mg) obtained at the process 6 of the above-mentioned example 34 one by one, 1-N sodium-hydroxide water solution (1ml) was added under ice-cooling, and it stirred for 30 minutes at 70 degrees C. Furthermore, concentrated hydrochloric acid (1ml) was added under ice-cooling stirring, and it stirred among the room temperature for 1 hour. After separating the depositing crystal and carrying out sequential washing under water (4ml) and chloroform (4ml), the heading compound (22.4mg, 82% of yield) of a brown crystal was obtained by carrying out reduced pressure drying.

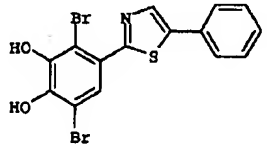
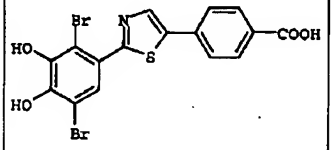
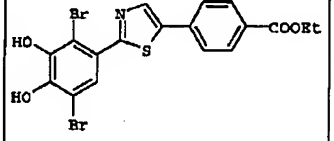
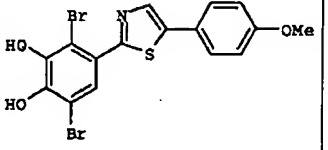
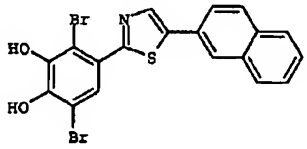
[0158] The compound of a publication was obtained to a table 9 thru/or a table 10 like the example 36 the example 34 of the example 42 above-mentioned thru/or the example 35.

[0159] As mentioned above, the compound manufactured in these examples 1 thru/or examples 42 is shown in a table 2 thru/or a table 10.

[0160]

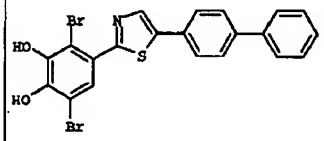
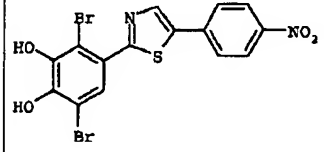
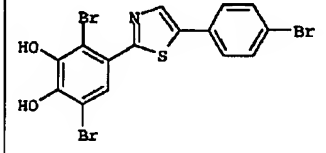
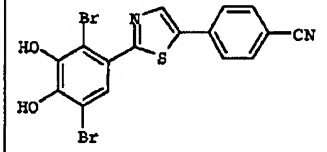
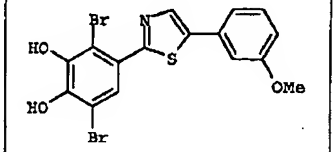
[A table 2]

表 2

実施例	化合物	融点 (℃)	^{1}H NMR (δ) ppm
1		203～204	DMSO-d_6 400 MHz 7.38 (1H, t, J=7.4Hz) 7.47 (2H, t, J=7.4Hz) 7.72 (1H, d, J=7.4Hz) 7.76 (1H, s) 8.32 (1H, s)
2		>260	DMSO-d_6 400 MHz 7.81 (1H, s) 7.88 (2H, d, J=8.4Hz) 8.01 (2H, d, J=8.4Hz) 8.47 (1H, s)
3		172.5～174.1	DMSO-d_6 400 MHz 1.34 (3H, t, J=7.4Hz) 4.34 (2H, q, J=8.6Hz) 7.81 (1H, s) 7.89 (2H, d, J=8.6Hz) 8.03 (2H, d, J=8.6Hz) 8.49 (1H, s)
4			DMSO-d_6 400 MHz 3.81 (3H, s) 7.03 (2H, d, J=8.9Hz) 7.65 (2H, d, J=8.9Hz) 7.74 (1H, s) 8.20 (1H, s) 9.91 (1H, brs) 10.14 (1H, brs)
5		192～195	DMSO-d_6 400 MHz 7.53-7.60 (2H, m) 7.82 (1H, s) 7.93 (2H, t, J=10.3Hz) 8.01 (2H, t, J=7.1Hz) 8.27 (1H, s) 8.48 (1H, s) 9.95 (1H, brs) 10.19 (1H, brs)

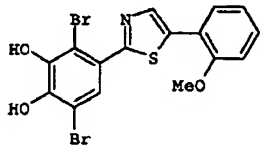
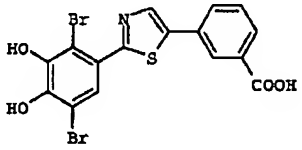
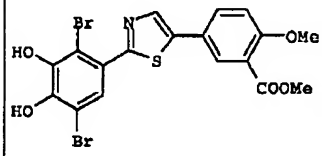
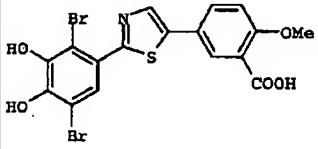
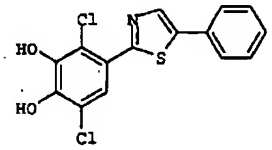
[0161]
[A table 3]

表 3

実施例	化合物	融点 (℃)	^{1}H NMR (δ) ppm
6		192～193	DMSO-d_6 400 MHz 7.40 (1H, t, J=7.7Hz) 7.50 (2H, t, J=7.7Hz) 7.71-7.88 (7H, m) 8.41 (1H, s) 9.85-10.30 (2H, brs)
7		221～224	DMSO-d_6 400 MHz 7.84 (1H, s) 8.03 (2H, d, J=8.9Hz) 8.31 (2H, d, J=8.9Hz) 8.60 (1H, s) 9.91-10.36 (2H, brs)
8		197.4～198.5	DMSO-d_6 400 MHz 7.65 (2H, d, J=8.9Hz) 7.68 (2H, d, J=8.9Hz) 7.75 (1H, s) 8.34 (1H, s)
9		>250	DMSO-d_6 400 MHz 7.78 (1H, s) 7.80 (4H, s like) 8.45 (1H, s)
10			DMSO-d_6 400 MHz 3.83 (3H, s) 6.87 (1H, dd, J=2.5, 7.8Hz) 7.26-7.29 (2H, m) 7.38 (1H, t, J=7.9Hz) 7.78 (1H, s) 8.35 (1H, s)

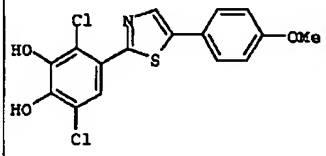
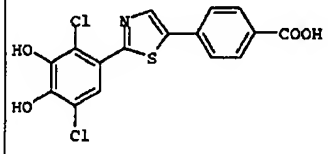
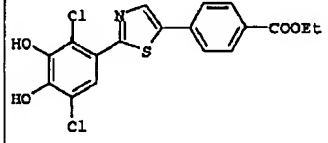
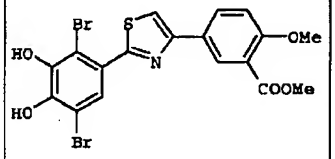
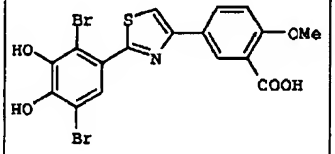
[0162]
[A table 4]

表 4

実施例	化合物	融点 (℃)	^{1}H NMR (δ) ppm
11			DMSO-d_6 400 MHz 3.94 (3H, s) 7.07 (1H, t, J=7.9Hz) 7.19 (1H, d, J=7.9Hz) 7.38 (1H, dt, J=2.0, 7.9Hz) 7.72 (1H, s) 7.83 (1H, dd, J=2.0, 7.9Hz) 8.39 (1H, s)
12		>250	DMSO-d_6 400 MHz 7.62 (1H, t, J=7.4Hz) 7.82 (1H, s) 7.95 (1H, d, J=7.4Hz) 8.03 (1H, d, J=7.4Hz) 8.20 (1H, s) 8.44 (1H, s)
13		140～144	DMSO-d_6 400 MHz 3.83 (3H, s) 3.88 (3H, s) 7.27 (1H, d, J=8.9Hz) 7.78 (1H, s) 7.91 (1H, dd, J=2.5, 8.9Hz) 7.92 (1H, s) 8.29 (1H, s) 9.92 (1H, brs) 10.17 (1H, brs)
14			DMSO-d_6 300 MHz 3.88 (3H, s) 7.24 (1H, d, J=8.8Hz) 7.79 (1H, s) 7.88 (1H, dd, J=2.6, 8.8Hz) 7.92 (1H, d, J=2.6Hz) 8.29 (1H, s) 9.94 (1H, brs) 10.19 (1H, brs)
15		203.8～205.6	DMSO-d_6 300 MHz 7.39 (1H, t, J=7.0Hz) 7.48 (2H, t, J=7.0Hz) 7.73 (1H, s) 7.75 (1H, d, J=7.0Hz) 8.35 (1H, s)

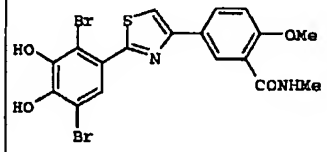
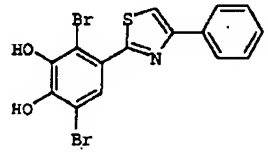
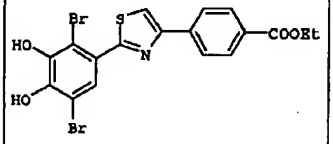
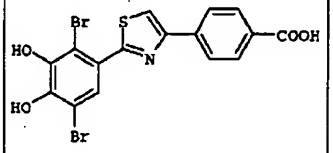
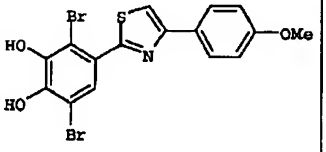
[0163]
[A table 5]

表 5

実施例	化合物	融点 (℃)	^{1}H NMR (δ) ppm
16		190.2～191.4	DMSO-d_6 300 MHz 3.80 (3H, s) 7.03 (2H, d, J=8.8Hz) 7.64 (2H, d, J=8.8Hz) 7.65 (1H, s) 8.14 (1H, s)
17		>250	DMSO-d_6 300 MHz 7.78 (1H, s) 7.87 (2H, d, J=8.4Hz) 8.01 (2H, d, J=8.4Hz) 8.49 (1H, s)
18		222.4～224.1	DMSO-d_6 400 MHz 1.34 (3H, t, J=7.2Hz) 4.34 (2H, q, J=7.2Hz) 7.74 (1H, s) 7.87 (2H, d, J=8.4Hz) 8.01 (2H, d, J=8.4Hz) 8.44 (1H, s)
19		151～155	DMSO-d_6 300 MHz 3.83 (3H, s) 3.88 (3H, s) 7.26 (1H, d, J=8.8Hz) 7.76 (1H, s) 8.18 (1H, s) 8.19 (1H, dd, J=2.5, 8.8Hz) 8.28 (1H, d, J=2.5 Hz)
20		137～139	DMSO-d_6 400 MHz 3.88 (3H, s) 7.23 (1H, d, J=8.9Hz) 7.78 (1H, s) 8.15 (1H, dd, J=2.5, 8.9Hz) 8.19 (1H, s) 8.27 (1H, d, J=2.5Hz) 9.92 (1H, brs) 10.16 (1H, brs) 12.74 (1H, brs)

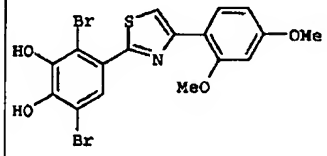
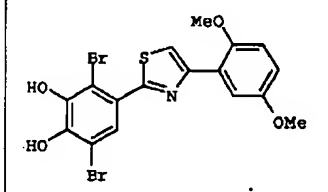
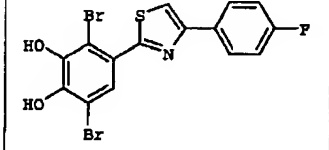
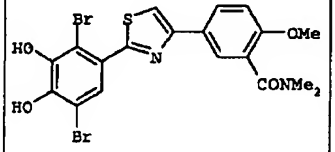
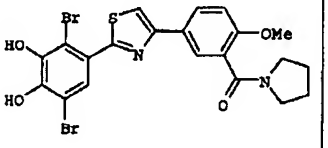
[0164]
[A table 6]

表 6

実施例	化合物	融点 (℃)	^{1}H NMR (δ) ppm
21		225～226	DMSO-d_6 300 MHz 2.83 (3H, d, J=4.4Hz) 3.93 (3H, s) 7.24 (1H, d, J=8.4Hz) 7.80 (1H, s) 8.10 (1H, dd, J=2.6, 8.4Hz) 8.17 (1H, s) 8.20 (1H, q, J=4.4Hz) 8.36 (1H, d, J=2.6Hz) 10.05 (1H, brs)
22		152～156	DMSO-d_6 400 MHz 7.37 (1H, t, J=7.4Hz) 7.47 (2H, t, J=7.4Hz) 7.80 (1H, s) 8.03 (1H, d, J=7.4Hz) 8.22 (1H, s)
23		152～155	DMSO-d_6 400 MHz 1.35 (3H, t, J=7.4Hz) 4.35 (2H, q, J=7.4Hz) 7.82 (1H, s) 8.05 (2H, d, J=8.4Hz) 8.15 (2H, d, J=8.4Hz) 8.44 (1H, s)
24		230	DMSO-d_6 400 MHz 7.82 (1H, s) 8.03 (2H, d, J=8.4Hz) 8.15 (2H, d, J=8.4Hz) 8.41 (1H, s)
25		166～167	DMSO-d_6 300 MHz 3.81 (3H, s) 7.04 (2H, d, J=8.8Hz) 7.80 (1H, s) 7.97 (2H, d, J=8.8Hz) 8.08 (1H, s) 10.04 (2H, brs)

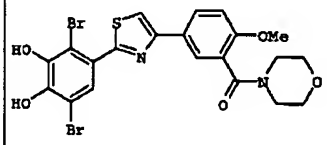
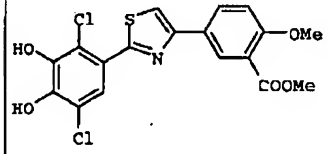
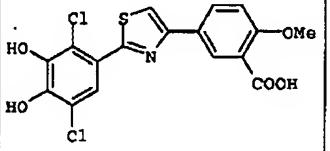
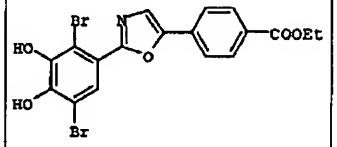
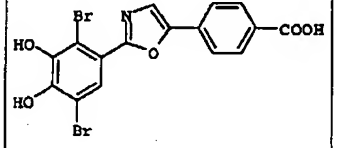
[0165]
[A table 7]

表 7

実施例	化合物	融点 (℃)	^{1}H NMR (δ) ppm
26		181～184	DMSO-d$_6$, 400 MHz 3.83 (3H, s) 3.94 (3H, s) 6.87 (1H, dd, J=2.5, 8.9Hz) 6.71 (1H, d, J=2.5Hz) 7.77 (1H, s) 8.02 (1H, s) 8.15 (1H, d, J=8.9Hz) 10.00 (2H, brs)
27			DMSO-d$_6$, 400 MHz 3.77 (3H, s) 3.89 (3H, s) 6.95 (1H, dd, J=3.5, 8.9Hz) 7.10 (1H, d, J=8.9Hz) 7.75 (1H, s) 7.77 (1H, d, J=3.5Hz) 8.21 (1H, s) 9.80-10.23 (2H, brs)
28		144～148	DMSO-d$_6$, 400 MHz 7.31 (2H, t, J=8.9Hz) 7.82 (1H, s) 8.09 (2H, dd, J=5.4, 8.9Hz) 8.23 (1H, s) 10.05 (2H, brs)
29		218～220	DMSO-d$_6$, 300 MHz 2.80 (3H, s) 3.00 (3H, s) 3.88 (3H, s) 7.19 (1H, d, J=8.8Hz) 7.78 (1H, s) 7.82 (1H, d, J=2.2Hz) 8.08 (1H, dd, J=2.2, 8.8Hz) 8.18 (1H, s)
30			DMSO-d$_6$, 400 MHz 1.76-1.91 (4H, m) 3.47 (2H, t, J=6.9Hz) 3.85 (3H, s) 7.18 (1H, d, J=8.4Hz) 7.77 (1H, s) 7.83 (1H, d, J=2.5Hz) 8.04 (1H, dd, J=2.5, 8.4Hz) 8.15 (1H, s)

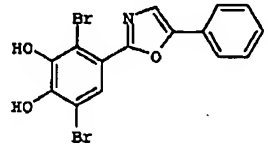
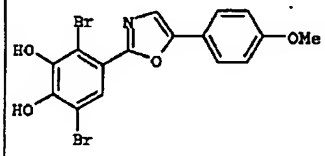
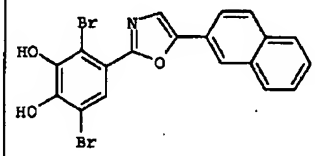
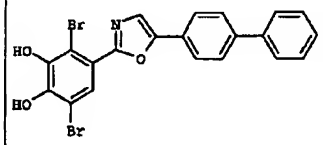
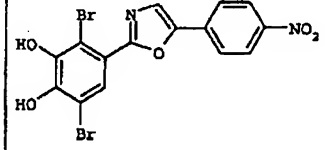
[0166]
[A table 8]

表 8

実施例	化合物	融点 (℃)	^{1}H NMR (δ) ppm
31		140～144	DMSO-d_6 400 MHz 3.16-3.21 (2H, m) 3.53 (2H, t, J=5.1Hz) 3.60-3.71 (4H, m) 3.86 (3H, s) 7.19 (1H, d, J=8.7Hz) 7.78 (1H, s) 7.85 (1H, d, J=2.6Hz) 8.06 (1H, dd, J=2.6, 8.7Hz) 8.18 (1H, s) 9.99 (2H, brs)
32		186.2～188.5	DMSO-d_6 400 MHz 3.84 (3H, s) 3.88 (3H, s) 7.26 (1H, d, J=8.5Hz) 7.80 (1H, s) 8.19 (1H, s) 8.20 (1H, d, J=7.65Hz) 8.28 (1H, s) 10.04 (1H, brs) 10.28 (1H, brs)
33		222.5～224.5	DMSO-d_6 400 MHz 3.88 (3H, s) 7.23 (1H, d, J=8.5Hz) 7.80 (1H, s) 8.16 (1H, d, J=8.5Hz) 8.20 (1H, s) 8.29 (1H, s) 10.04 (1H, brs) 10.27 (1H, brs)
34		207.2～209.3	DMSO-d_6 400 MHz 1.34 (3H, t, J=8.2Hz) 4.33 (2H, q, d=8.2Hz) 7.60 (1H, s) 7.90 (2H, d, J=8.4Hz) 8.02 (2H, d, J=8.4Hz) 8.29 (1H, s)
35		>250	DMSO-d_6 300 MHz 7.72 (1H, s) 7.93 (2H, d, J=8.4Hz) 8.02 (2H, d, J=8.4Hz) 8.07 (1H, s)

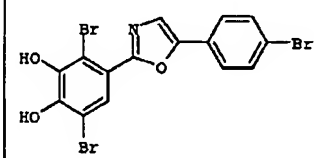
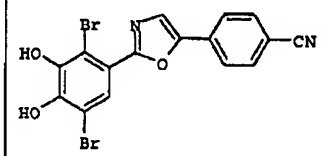
[0167]
[A table 9]

表 9

実施例	化合物	融点 (℃)	^{1}H NMR (δ) ppm
36		208～211	DMSO-d_6 400 MHz 7.39 (1H, t, J=7.4Hz) 7.50 (2H, t, J=7.4Hz) 7.68 (1H, s) 7.81 (1H, d, J=7.4Hz) 7.83 (1H, s) 10.12 (2H, brs)
37		160～161	DMSO-d_6 300 MHz 3.80 (3H, s) 7.05 (2H, d, J=8.8Hz) 7.48 (1H, s) 7.55 (1H, s) 7.69 (2H, d, J=8.8Hz)
38		214～217	DMSO-d_6 300 MHz 7.49-7.59 (2H, m) 7.59 (1H, s) 7.85 (1H, s) 7.88-8.05 (4H, m) 8.28 (1H, s)
39		215～217	DMSO-d_6 300 MHz 7.39 (1H, t, J=7.0Hz) 7.50 (2H, t, J=7.0Hz) 7.60 (1H, s) 7.74 (2H, d, J=7.0Hz) 7.81 (2H, d, J=8.4Hz) 7.81 (1H, s) 7.87 (2H, d, J=8.4Hz)
40		>250	DMSO-d_6 400 MHz 7.76 (1H, s) 8.08 (2H, d, J=8.9Hz) 8.15 (1H, s) 8.35 (2H, d, J=8.9Hz)

[0168]
[A table 10]

表 10

実施例	化合物	融点 (℃)	^{1}H NMR (δ) ppm
41		197.5～198.6	DMSO-d_6 400 MHz 7.61 (1H, s) 7.66 (2H, d, J=8.4Hz) 7.70 (2H, d, J=8.4Hz) 7.74 (1H, s)
42		>250	DMSO-d_6 400 MHz 7.74 (1H, s) 7.98 (2H, d, J=8.5Hz) 8.00 (2H, d, J=8.5Hz) 8.08 (1H, s)

[0169] Next, the result of the trial which followed the protein thyrosin phosphatase 1B inhibitory action

of this invention is shown.
(Example of a trial)
The example 1 (protein thyrosin phosphatase 1B inhibitory action) of a trial
- Preparation of the assay buffer solution : 50mM The Tris-HCl buffer solution (pH7.5), 50mM NaCl and 3mM(s) Dithiothreitol (DTT) was prepared.
- Preparation of a specimen : they are 10mM(s) of the trial compound of 0.1, 0.3, 1 and 3, and 10microM, respectively so that the last dimethyl sulfoxide (DMSO) concentration may become 1% or less. The DMSO solution was diluted with the above-mentioned assay buffer solution. In addition, the assay buffer solution was used as control.
- Preparation of a substrate : the synthetic peptide which carried out phosphorylation of the three thyrosins from 12 amino acid to the arrays 1142-1153 of an insulin receptor was diluted with the above-mentioned assay buffer solution, and it prepared to 80microM.
- Preparation of an enzyme : recombinant Homo sapiens protein thyrosin phosphatase 1B made from UBI was diluted with the above-mentioned assay buffer solution (0.01 thru/or 0.08microg/25microl).
(The assessment approach) Specimen prepared on 96 hole plate as above-mentioned 10microl and substrate Enzyme which carried out sequential addition and prepared 25microl as above-mentioned 25microl was added and it mixed. Malachite Green which is the Lynn color coupler after incubating for 10 minutes at 37 degrees C (Biomol) 120microl is added, and it incubated for 20 minutes and was made to color at a room temperature further. The absorbance of 650nm was measured for this with the plate reader, and the protein thyrosin phosphatase 1B inhibitory action of a trial compound was evaluated. The result was shown in a table 11 thru/or a table 12.
[0170] The example 2 (measurement of a blood sugar decreasing rate) of a trial
0.5% methyl cellulose suspension of a trial compound was administered orally to 6 thru/or the 9-weeks old male ob/ob mouse which carried out the group division with the blood sugar level at the time of gluttony for 1 time per and five days day. In addition, the control group was medicated only with the methyl cellulose solution 0.5%. Blood collecting was performed from eyegrounds to the bottom of the two times of 8 thru/or 9 hours [the day / of trial compound administration / 5th / administration 3 thru/or 4 hours, and] after, and anesthesia. In addition, blood collecting extracted food just before trial compound administration, and was performed under the fast. Thus, after carrying out centrifugal separation of the extracted blood, the blood sugar level was measured using the hexokinase method (glucose measurement kit) from the obtained plasma. Assessment showed the decreasing rate of the blood sugar level of the trial compound administration group to a control group by %. The result was shown in a table 11 thru/or a table 12.
[0171]
[A table 11]

表 11

実施例	PTP1B阻害作用 (IC_{50} : μM)	血糖低下率 (%)		
		用量 (mg/kg)	3-4 hr.	8-9 hr.
1	0.54	3	45	44
		10	45	44
2	0.64	3	33	27
		10	39	28
4	0.67			
9	0.59			
10	0.62			
12	0.83	3	28	10
		10	33	24
14	0.91			
15	0.44			
16	0.58			
17	0.77			
19	0.46	3	24	10
		10	29	18
22	0.74			

[0172]
[A table 12]

表 12

実施例	PTP1B 阻害作用 (IC_{50} : μM)	血糖低下率 (%)		
		用量 (mg/kg)	3-4 hr.	8-9 hr.
25	0.55	3	19	29
		10	30	10
26	0.7			
27	0.62			
28	0.55			
29	0.97	3	32	10
		10	36	12
30	0.85			
31	0.82			
32	0.65			
35	0.77			
37	0.65			
41	0.88			

[0173]
[Effect of the Invention] By the above test result etc., the compound [I] concerning this invention has the outstanding PTP1B inhibitory action. That is, it is expected as prevention or the remedy of the diabetes mellitus new type which can improve an insulin operation directly and can improve insulin susceptibility, insulin resistance, and/or glucose tolerance. Moreover, it is expected also as prevention or the remedy of the complication, and a remedy of a disease with which PTP1B intervenes further.

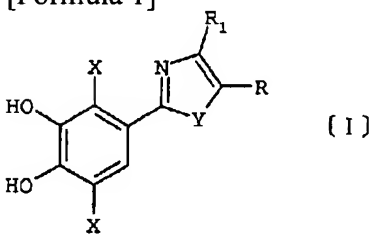
[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] General formula [I]
[Formula 1]



[I]

R or one side of R1 is a hydrogen atom among [type. Another side It is the hetero aryl group of 1 5 which it has three pieces and which may be permuted thru/or 6 members about the heteroatom chosen from the aryl group which may be permuted or a nitrogen atom, an oxygen atom, and a sulfur atom. It is the salt which X is a halogen atom and can permit Y on a sulfur atom, an oxygen atom, 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound expressed with] which is -NR2- (it is here and R2 is a hydrogen atom or C1-4 alkyl group), or its remedy.
[Claim 2] You may permute by the identitas as which R or one side of R1 is a hydrogen atom, and another side is chosen from the following or 1 which may differ thru/or three substituents. An aryl group or a nitrogen atom, The heteroatom chosen from an oxygen atom and a sulfur atom 1 -- or Even if the hetero aryl group permutation of 5 which it has three pieces thru/or the 6 members is carried out Good C1-4 alkyl group; even if it permutes good C1-4 alkoxy-group; -- C1-4 alkylthio-group; -- C1-4 alkyl sulfinyl group; -- C1-4 alkyl sulfonyl group; -- amino sulfonyl group; -- halogen atom; -- nitro group; -- cyano group; -- carboxyl group; -- C2-5 alkoxy carbonyl group; -NR3R4;-N (R5) CONR3R4;-N(R5) COR6;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, It is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members. R5 is a hydrogen atom or C1-4 alkyl group, and R6 is C1-4 alkyl group or C1-4 alkoxy group -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 or its remedy.
[Claim 3] R or one side of R1 is a hydrogen atom. The aryl group C1-4 alkoxy-group; halogen atom; nitro group; cyano group as which another side is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 2 or its remedy.

[Claim 4] The aryl group methoxy group as which R or one side of R1 is a hydrogen atom, and another side is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; A fluorine atom, bromine atom; -- nitro group; -- cyano group; -- carboxyl group; -- a methoxycarbonyl group -- Ethoxycarbonyl radical; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 3 which is a methyl carbamoyl group, a dimethyl carbamoyl group, a pyrrolidinyl carbonyl group, and a morpholino carbonyl radical, or its remedy.
[Claim 5] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 to 4 whose R1 is a hydrogen atom, or its remedy.
[Claim 6] The phenyl group C1-4 alkoxy-group; halogen atom; nitro group; cyano group as which R is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 3 or its remedy.
[Claim 7] The phenyl group C1-4 alkoxy-group; halogen atom; nitro group; cyano group as which R is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 6 which is a carboxyl group;C2-5 alkoxy carbonyl group, or its remedy.
[Claim 8] The phenyl group methoxy group; bromine atom; nitro group; cyano group; carboxyl group as which R is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 7 which is a methoxycarbonyl group and an ethoxycarbonyl radical, or its remedy.
[Claim 9] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 8 whose R is a phenyl group, 2-methoxypheny radical, 3-methoxypheny radical, 4-methoxypheny radical, 4-BUROMO phenyl group, 4-nitrophenyl group, 4-cyanophenyl radical, 3-carboxyphenyl radical, 4-carboxyphenyl radical, 4-ethoxycarbonyl phenyl group, a 3-carboxy-4-methoxycarbonyl phenyl group, and a 4-methoxy-3-methoxycarbonyl phenyl group, or its remedy.
[Claim 10] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 9 whose R is a phenyl group and 4-carboxyphenyl radical, or its remedy.
[Claim 11] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 to 4 whose R is a hydrogen atom, or its remedy.
[Claim 12] The phenyl group C1-4 alkoxy-group; halogen atom; nitro group; cyano group as which R1 is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 3 or its remedy.
[Claim 13] The phenyl group C1-4 alkoxy-group; halogen atom with which R1 is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group;-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 12 or its remedy.

[Claim 14] The phenyl group methoxy group; fluorine atom; carboxyl group; methoxycarbonyl group, ethoxycarbonyl radical as which R1 is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 13 which is a methyl carbamoyl group, a dimethyl carbamoyl group, a pyrrolidinyl carbamoyl group, and a morpholino carbamoyl group, or its remedy.
[Claim 15] R1 A phenyl group, 4-methoxypheny radical, 4-fluoro phenyl group, 4-carboxyphenyl radical, 4-ethoxycarbonyl phenyl group, 2, 4-dimethoxy phenyl group, 2, 5-dimethoxy phenyl group, a 3-carboxy-4-methoxypheny radical, A 4-methoxy-3-methoxycarbonyl phenyl group, a 4-methoxy-3-(methyl carbamoyl) phenyl group, A 3-(dimethyl carbamoyl)-4-methoxypheny radical, a 4-methoxy-3-(1-pyrrolidinyl carbonyl) phenyl group, The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 14 which is a 4-methoxy-3-(morpholino carbonyl) phenyl group, or its remedy.
[Claim 16] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 15 whose R1 is a 4-methoxy-3-methoxycarbonyl phenyl group, or its remedy.
[Claim 17] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 to 16 whose Y is a sulfur atom, or its remedy.
[Claim 18] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 to 16 whose Y is an oxygen atom, or its remedy.
[Claim 19] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 to 16 whose Y is -NR2- (here, R2 is a hydrogen atom or C1-4 alkyl group), or its remedy.
[Claim 20] The phenyl group C1-4 alkoxy-group; halogen atom; nitro group; cyano group as which R is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 3 whose R1 are a carboxyl group;C2-5 alkoxy carbonyl group and is a hydrogen atom, and whose Y is a sulfur atom, or its remedy.
[Claim 21] The phenyl group methoxy group; bromine atom; nitro group; cyano group; carboxyl group as which R is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 20 whose R1 are a methoxycarbonyl group and an ethoxycarbonyl radical and is a hydrogen atom, and whose Y is a sulfur atom, or its remedy.
[Claim 22] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 21 whose R is a phenyl group or 4-carboxyphenyl radical, whose R1 is a hydrogen atom, and whose Y is a sulfur atom, or its remedy.
[Claim 23] The phenyl group C1-4 alkoxy-group; halogen atom with which R is a hydrogen atom and R1 is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; carboxyl group;C2-5 alkoxy carbonyl group-CONR three R4 (here) R3 and R4 are the same -- or -- differing -- **** -- a hydrogen atom and C -- one to 4 alkyl group It becomes together with the nitrogen atom which R3 and R4 combine. Further Or a nitrogen atom, it is the heterocycle radical of 5 which may contain the heteroatom chosen from an oxygen atom and a sulfur atom thru/or 6 members -- it is -- the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 3 whose Y is a sulfur atom, or its remedy.
[Claim 24] The phenyl group methoxy group; fluorine atom; carboxyl group; methoxycarbonyl group, ethoxycarbonyl radical as which R is a hydrogen atom and R1 is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 23 whose Y it is a methyl carbamoyl group, a dimethyl carbamoyl group, a pyrrolidinyl carbonyl group, and a morpholino carbonyl radical, and is a sulfur atom, or its remedy.
[Claim 25] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole

compound according to claim 24 whose R is a hydrogen atom, whose R1 is a 4-methoxy-3-methoxycarbonyl phenyl group, and whose Y is a sulfur atom, or its remedy.
[Claim 26] The phenyl group C1-4 alkoxy-group; halogen atom; nitro group; cyano group as which R is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 3 whose R1 are a carboxyl group;C2-5 alkoxy carbonyl group and is a hydrogen atom, and whose Y is an oxygen atom, or its remedy.
[Claim 27] The phenyl group methoxy group; bromine atom; nitro group; cyano group; carboxyl group as which R is chosen from the following and which may be permuted by the same or 1 which may differ thru/or three substituents; the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 26 whose R1 are an ethoxycarbonyl radical and is a hydrogen atom, and whose Y is an oxygen atom, or its remedy.
[Claim 28] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 to 27 whose X is a chlorine atom or a bromine atom, or its remedy.
[Claim 29] A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl thiazole, A 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-naphthyl) thiazole, A 5-(4-biphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-nitrophenyl) thiazole, A 5-(4-BUROMO phenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 5-(4-cyanophenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(3-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-methoxypheny) thiazole, A 5-(3-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo 3, 4-dihydroxy phenyl)-5-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 5-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-phenyl thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) thiazole, A 5-(4-carboxyphenyl)-2-(2, 5-dichloro -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-phenyl thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-ethoxycarbonyl phenyl) thiazole, A 4-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(2, 4-dimethoxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(2, 5-dimethoxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-fluoro phenyl) thiazole, A 4-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo 3, 4-dihydroxy phenyl)-4-[3-(dimethyl carbamoyl)-4-methoxypheny] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(1-pyrrolidinyl carbonyl) phenyl] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(methyl carbamoyl) phenyl] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(morpholino carbonyl) phenyl] thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 4-(3-carboxy-4-methoxypheny)-2-(2, 5-dichloro -3, 4-dihydroxy phenyl) thiazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) oxazole, 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-naphthyl) oxazole, 5-(4-biphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-nitrophenyl) oxazole, 5-(4-BUROMO phenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, And the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 chosen from the group which consists of 5-(4-cyanophenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, or its remedy.
[Claim 30] A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl thiazole, A 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-

ethoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-naphthyl) thiazole, A 5-(4-biphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-nitrophenyl) thiazole, A 5-(4-BUROMO phenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 5-(4-cyanophenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(3-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-methoxypheny) thiazole, A 5-(3-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo 3, 4-dihydroxy phenyl)-5-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 5-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-phenyl thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) thiazole, A 5-(4-carboxyphenyl)-2-(2, 5-dichloro -3, 4-dihydroxy phenyl) thiazole, And 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 29 chosen from the group which consists of a 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) thiazole Or the salt which can be permitted on the remedy.

[Claim 31] A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-phenyl thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-ethoxycarbonyl phenyl) thiazole, A 4-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxypheny) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(2, 4-dimethoxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(2, 5-dimethoxy phenyl) thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-fluoro phenyl) thiazole, A 4-(3-carboxy-4-methoxypheny)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, A 2-(2, 5-dibromo 3, 4-dihydroxy phenyl)-4-[3-(dimethyl carbamoyl)-4-methoxypheny] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(1-pyrrolidinyl carbonyl) phenyl] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(methyl carbamoyl) phenyl] thiazole, A 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-[4-methoxy-3-(morpholino carbonyl) phenyl] thiazole, A 2-(2, 5-dichloro -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, And 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 29 chosen from the group which consists of a 4-(3-carboxy-4-methoxypheny)-2-(2, 5-dichloro -3, 4-dihydroxy phenyl) thiazole Or the salt which can be permitted on the remedy.

[Claim 32] 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-ethoxycarbonyl phenyl) oxazole, 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-methoxypheny) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(2-naphthyl) oxazole, 5-(4-biphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-(4-nitrophenyl) oxazole, 5-(4-BUROMO phenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, And the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 29 chosen from the group which consists of 5-(4-cyanophenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) oxazole, or its remedy.

[Claim 33] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 30 which is a 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-5-phenyl thiazole, or its remedy.

[Claim 34] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 30 which is a 5-(4-carboxyphenyl)-2-(2, 5-dibromo -3, 4-dihydroxy phenyl) thiazole, or its remedy.

[Claim 35] The salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 31 which is a 2-(2, 5-dibromo -3, 4-dihydroxy phenyl)-4-(4-methoxy-3-methoxycarbonyl phenyl) thiazole, or its remedy.

[Claim 36] The remedy constituent which becomes considering the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 to 35 or its remedy as an active principle.

[Claim 37] The protein thyrosin phosphatase 1B inhibitor which becomes considering the salt which can

be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 to 35 or its remedy as an active principle.
[Claim 38] Diabetic medicine which becomes considering the salt which can be permitted on 2-(2, 5-dihalogen -3, 4-dihydroxy phenyl) azole compound according to claim 1 to 35 or its remedy as an active principle.

[Translation done.]